Weill Cornell Medicine

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Institute of Artificial Intelligence for Digital Health

Disentangling the Clinical Complexity of Heterogeneous Diseases Through Data-Driven Subphenotyping with Large Scale Electronic Health Records

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https://wcm-wanglab.github.io/index.html

Outline

- Introduction
- Subphenotyping of COVID-19 at infection confirmation
- Subphenotyping of Severe COVID-19 after Mechanical Ventilation
- Subphenotyping of Long COVID
- Discussions

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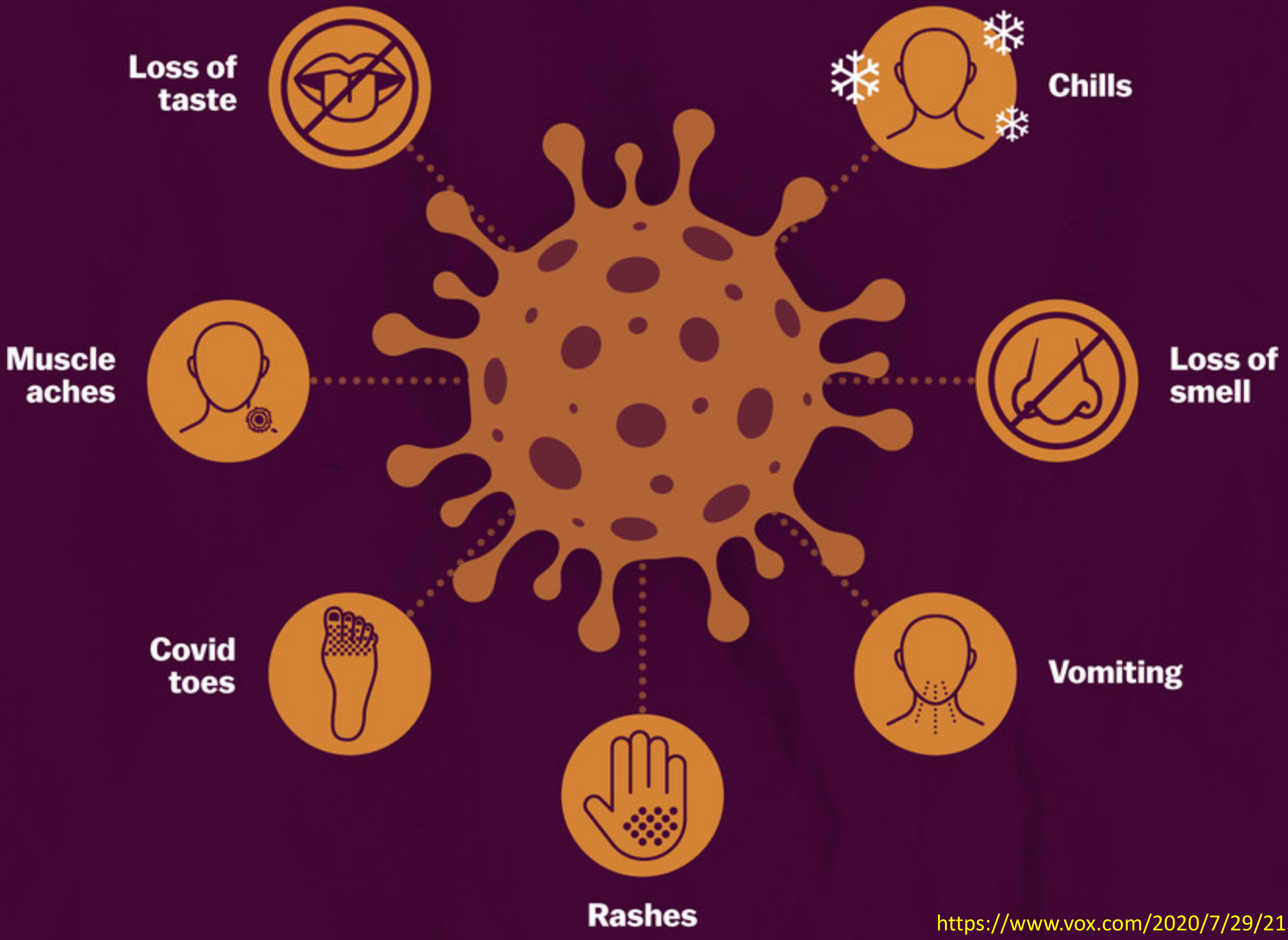
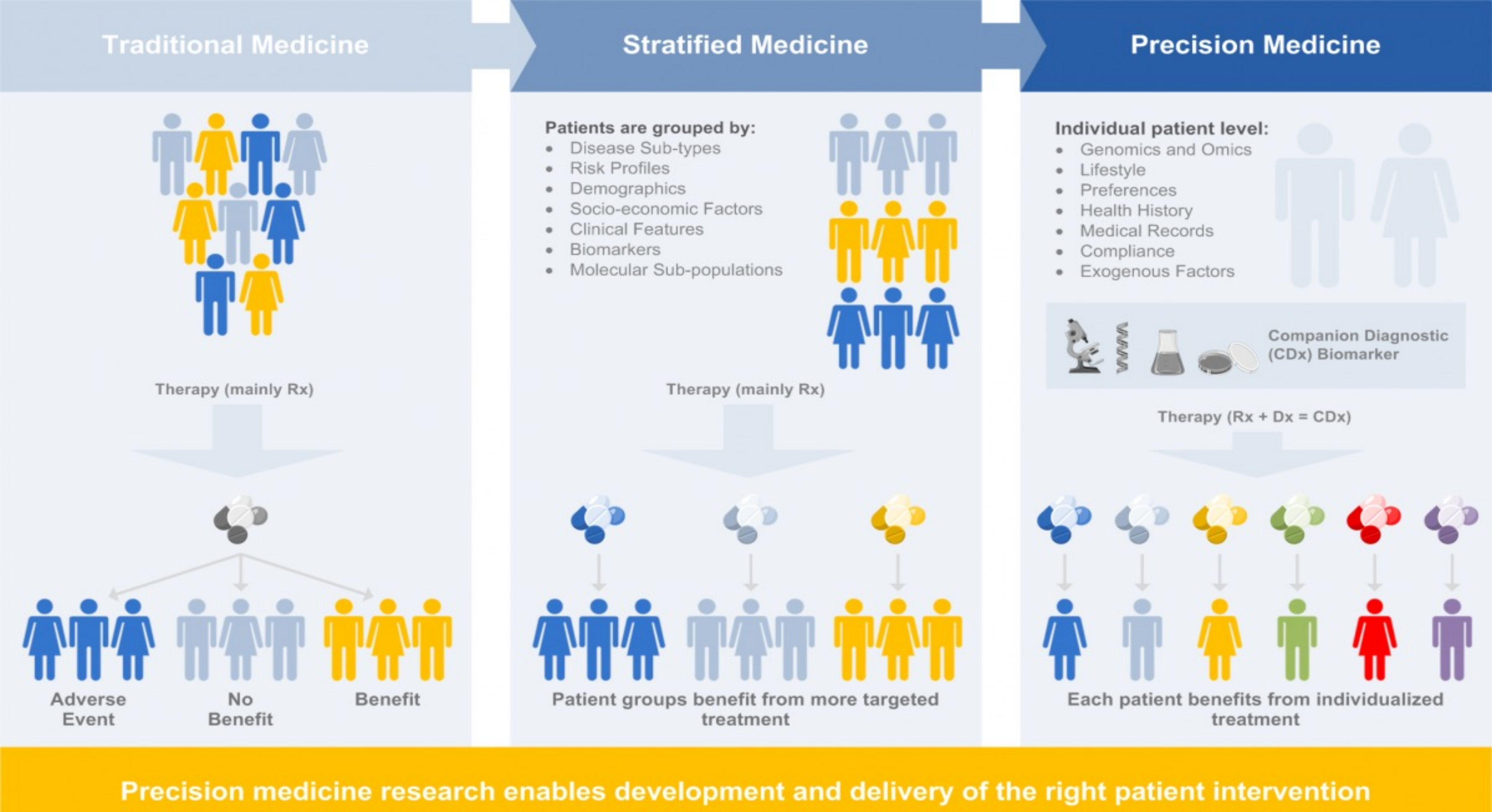


https://www.vox.com/2020/7/29/21327317/symptoms-of-covid-19-coronavirus-fever-cough-toes-rash-loss-of-taste-smell

https://www.clinicaladvisor.com/home/topics/infectious-diseases-information-center/long-covid-diagnosis-treatment/



https://www.linguamatics.com/solutions/precision-medicine

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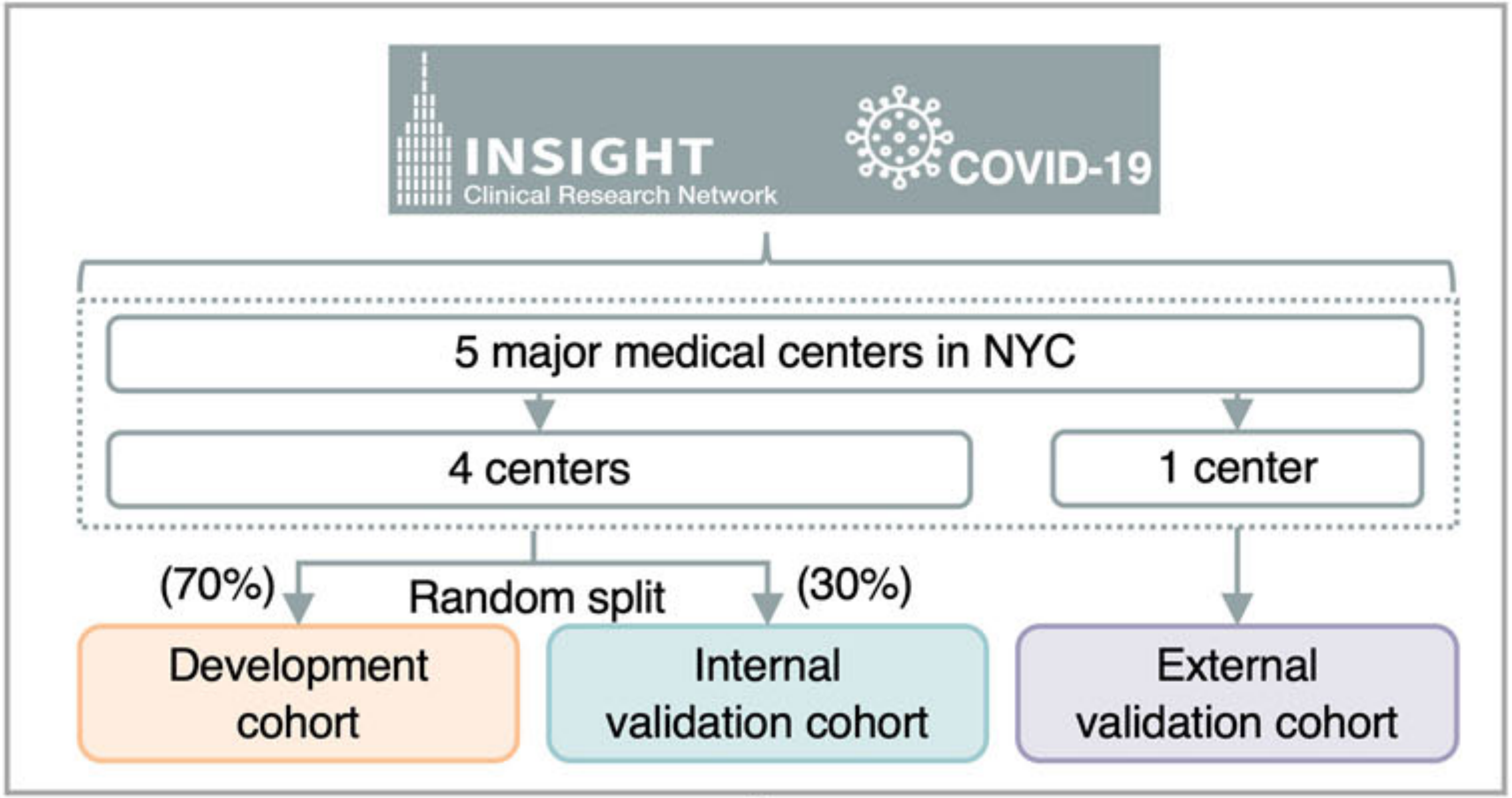
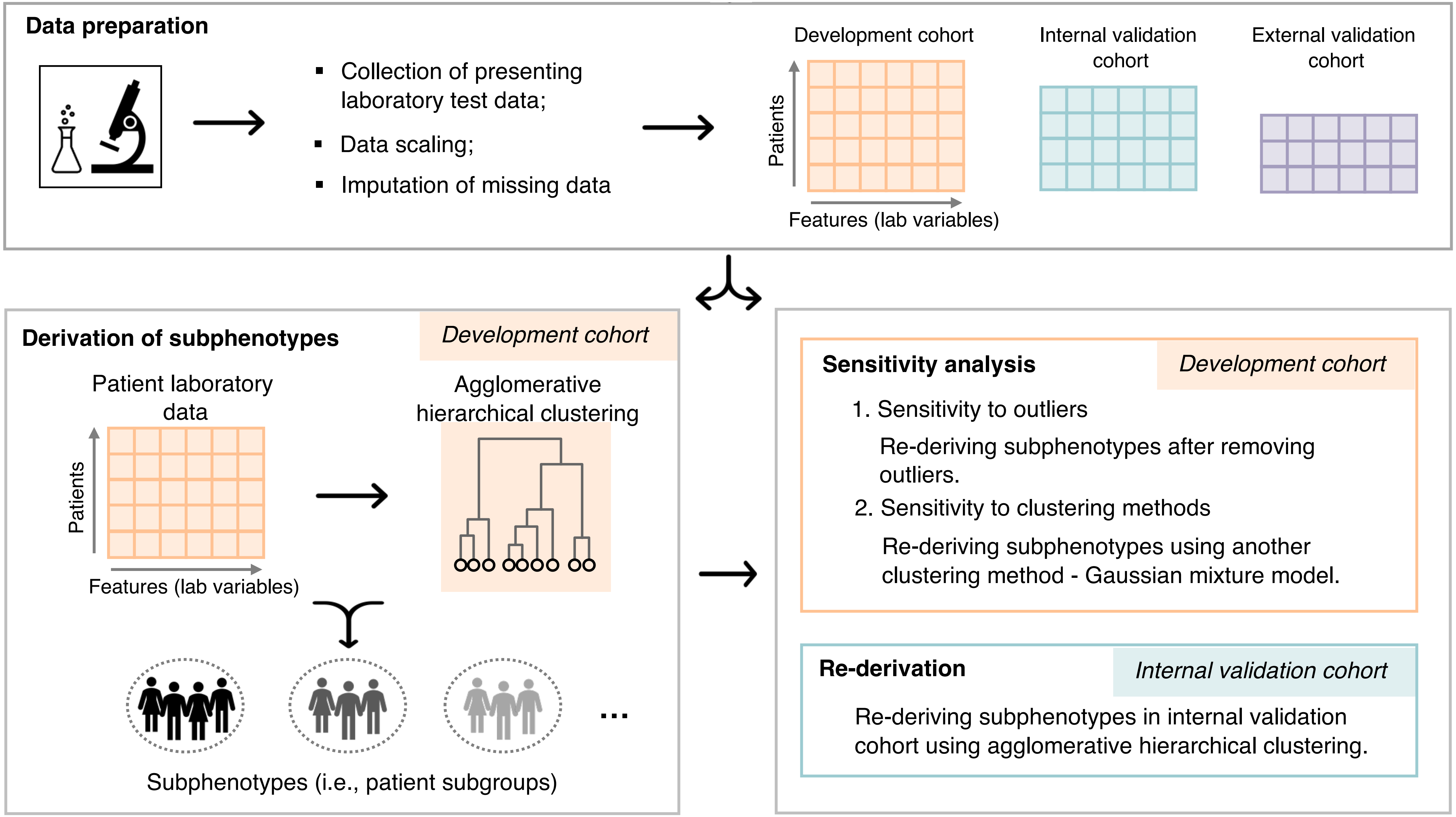
- Subphenotyping of COVID-19 at infection confirmation
- Subphenotyping of Severe COVID-19 after Mechanical Ventilation
- Subphenotyping of Long COVID
- Subphenotyping of AD
- Discussions

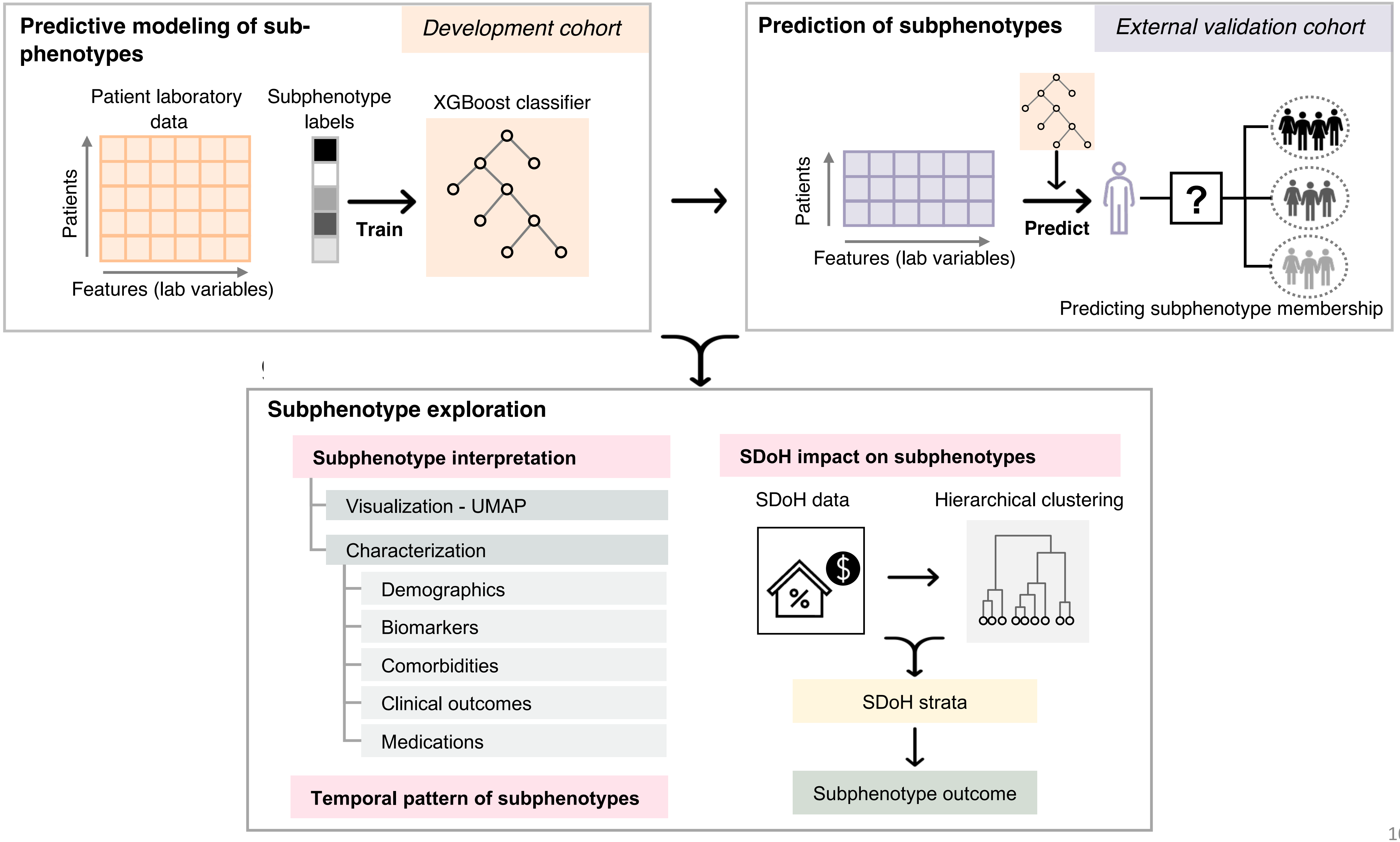
Su, Chang, Yongkang Zhang, James H. Flory, Mark G. Weiner, Rainu Kaushal, Edward J. Schenck, and Fei Wang. "Clinical subphenotypes in COVID-19: derivation, validation, prediction, temporal patterns, and interaction with social determinants of health." *NPJ digital medicine* 4, no. 1 (2021): 110.

Overall Setup



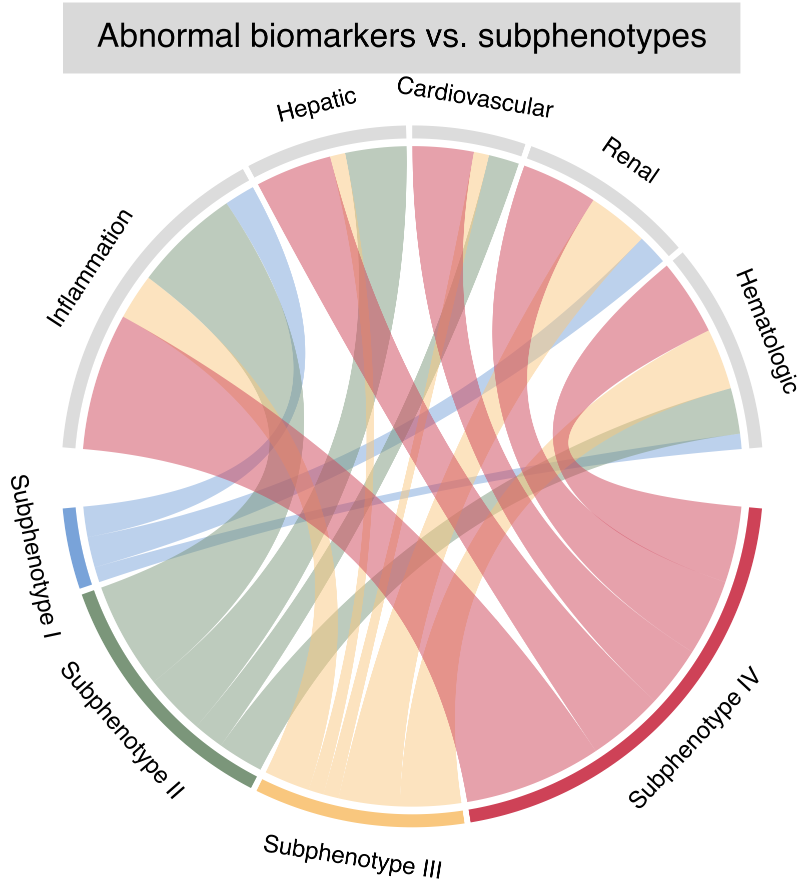
Kaushal, Rainu, George Hripcsak, Deborah D. Ascheim, Toby Bloom, Thomas R. Campion Jr, Arthur L. Caplan, Brian P. Currie et al. "Changing the research landscape: the new York City clinical data research network." *Journal of the American Medical Informatics Association* 21, no. 4 (2014): 587-590.

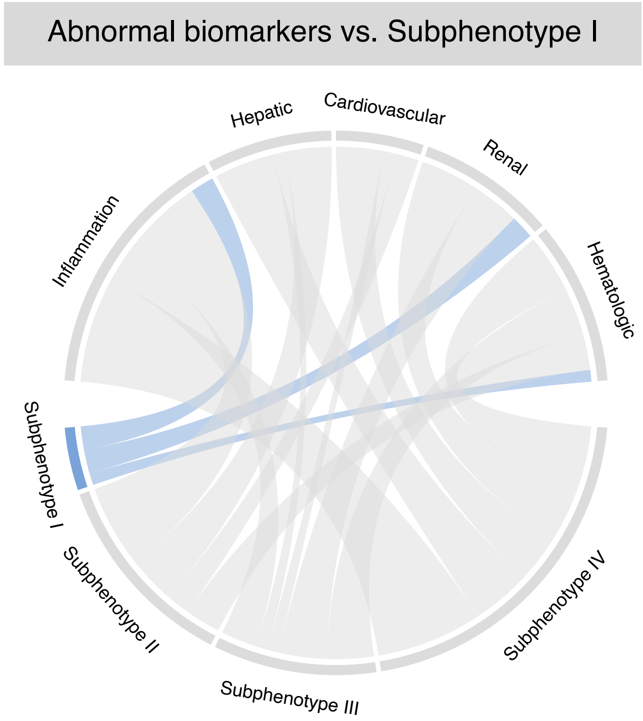

Data preparation
Collection of presenting laboratory test data;
Data scaling;
Imputation of missing data
Development cohort
Internal validation cohort
External validation cohort
Patients
Features (lab variables)
Derivation of subphenotypes
Development cohort
Patient laboratory data
Patients
Features (lab variables)
Agglomerative hierarchical clustering
...
Subphenotypes (i.e., patient subgroups)
Sensitivity analysis
Development cohort
1. Sensitivity to outliers
Re-deriving subphenotypes after removing outliers.
2. Sensitivity to clustering methods
Re-deriving subphenotypes using another clustering method - Gaussian mixture model.
Re-derivation
Internal validation cohort
Re-deriving subphenotypes in internal validation cohort using agglomerative hierarchical clustering.

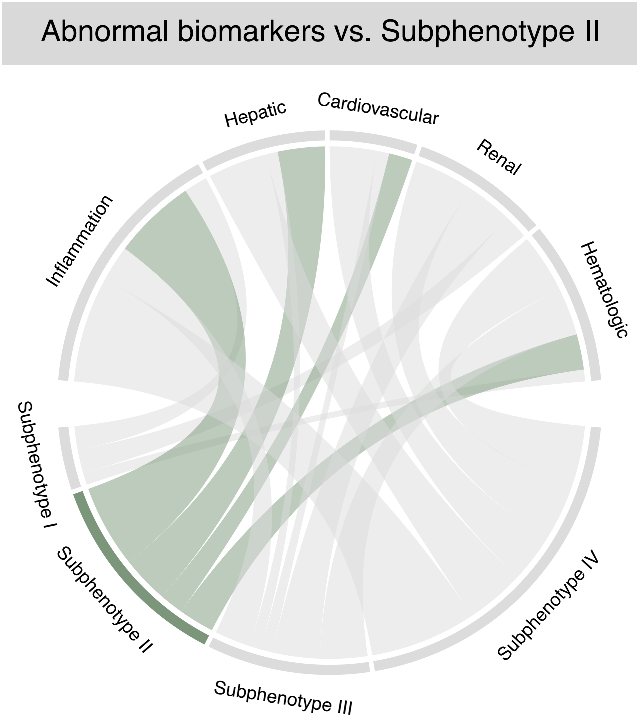

Predictive modeling of sub-phenotypes
Development cohort
Patient laboratory data
Subphenotype labels
XGBoost classifier
Patients
Features (lab variables)
Train
Prediction of subphenotypes
External validation cohort
Patients
Features (lab variables)
Predict
?
Predicting subphenotype membership
Subphenotype exploration
Subphenotype interpretation
Visualization - UMAP
Characterization
Demographics
Biomarkers
Comorbidities
Clinical outcomes
Medications
Temporal pattern of subphenotypes
SDoH impact on subphenotypes
SDoH data
Hierarchical clustering
%
$
SDoH strata
Subphenotype outcome

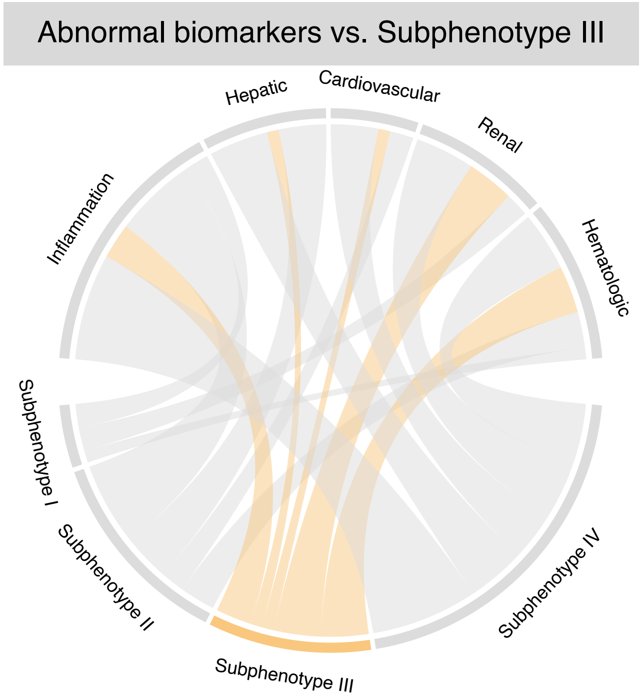
Cohort Characteristics

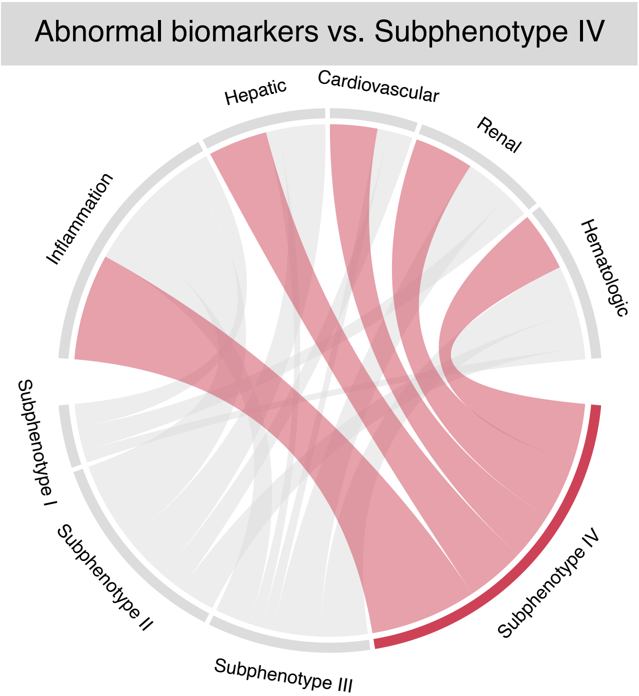
Characteristics	Cohort		
	Development cohort	Internal validation cohort	External validation cohort
No. of patients	8,199	3,519	2,700
Construction method	70% patients (randomly selected) from 4 sites of INSIGNT network: NYU-LMC, NYP-WCMC, MSHS, and MMC	Remaining 30% patients from 4 sites of INSIGNT network: NYU Langone Medical Center, NYP-WCMC, Mount Sinai Health System, and Montefiore Medical Center	NYP-CUMC
Age, y, Median (IQR)	63.53 [50.57 - 75.15]	63.51 [50.95 - 75.17]	65.58 (51.08 - 77.39)
Sex female, N (%)	3,787 (46.2)	1,585 (45.0)	1,305 (48.3)
Race, N (%)			
White	2,036 (24.8)	838 (23.8)	675 (25.0)
Black	2,155 (26.3)	915 (26.0)	545 (20.2)
Asian	409 (5.0)	193 (5.5)	28 (1.0)
Multiple race	39 (0.5)	13 (0.4)	912 (33.8)
Other/unknown	3560 (43.4)	1560 (44.3)	540 (20.0)
Outcomes (60 days), N (%)			
Mortality	1529 (18.65)	696 (19.78)	556 (20.59)
Mechanical ventilation (intubation	1154 (14.07)	497 (14.12)	248 (9.19)
ICU admission	1494 (18.22)	661 (18.78)	-


Abnormal biomarkers vs. subphenotypes
Inflammation
Hepatic
Cardiovascular
Renal
Hematologic
Subphenotype I
Subphenotype II
Subphenotype III
Subphenotype IV

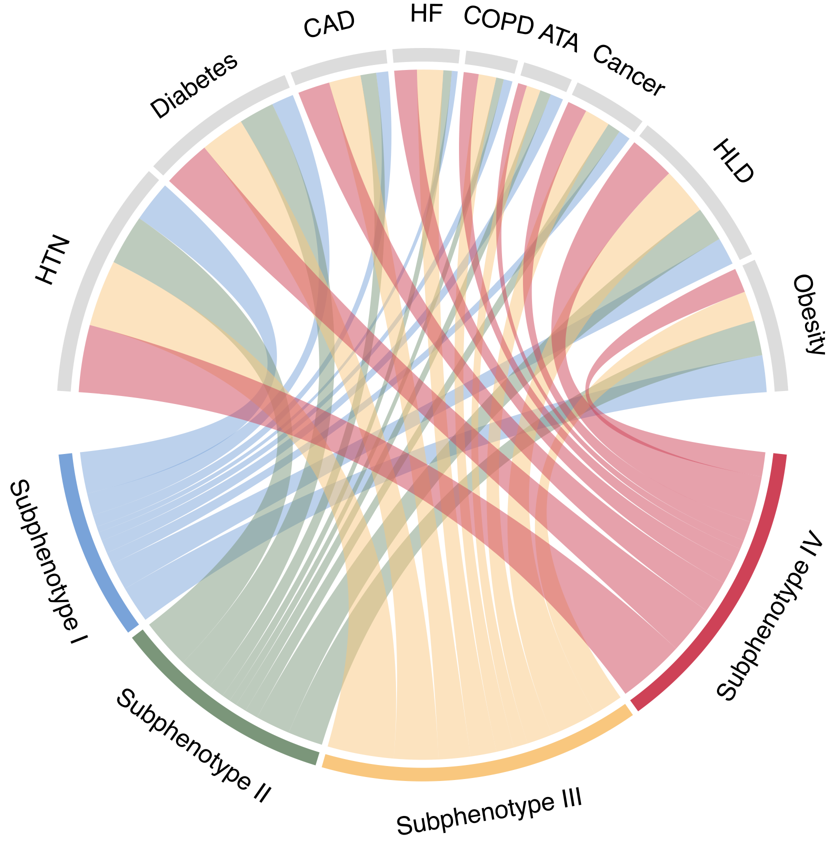

Abnormal biomarkers vs. Subphenotype I
Inflammation
Hepatic
Cardiovascular
Renal
Hematologic
Subphenotype I
Subphenotype II
Subphenotype III
Subphenotype IV


Abnormal biomarkers vs. Subphenotype II
Inflammation
Hepatic
Cardiovascular
Renal
Hematologic
Subphenotype I
Subphenotype II
Subphenotype III
Subphenotype IV

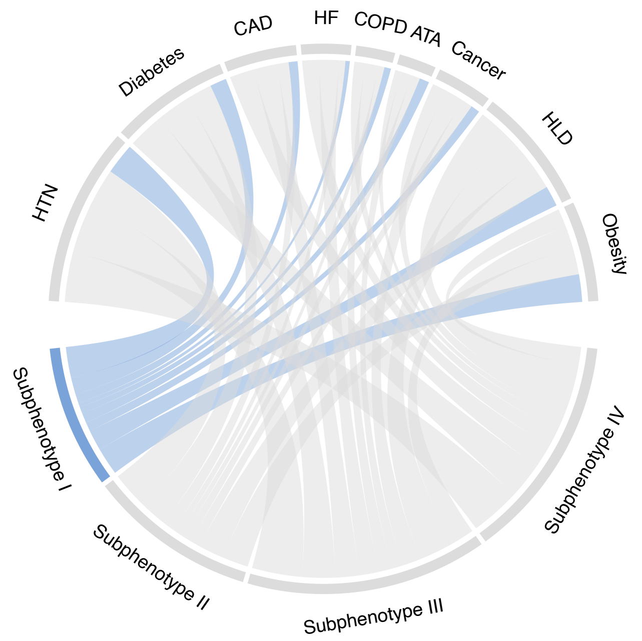

Abnormal biomarkers vs. Subphenotype III
Inflammation
Hepatic
Cardiovascular
Renal
Hematologic
Subphenotype I
Subphenotype II
Subphenotype III
Subphenotype IV


Abnormal biomarkers vs. Subphenotype IV
Inflammation
Hepatic
Cardiovascular
Renal
Hematologic
Subphenotype I
Subphenotype II
Subphenotype III
Subphenotype IV

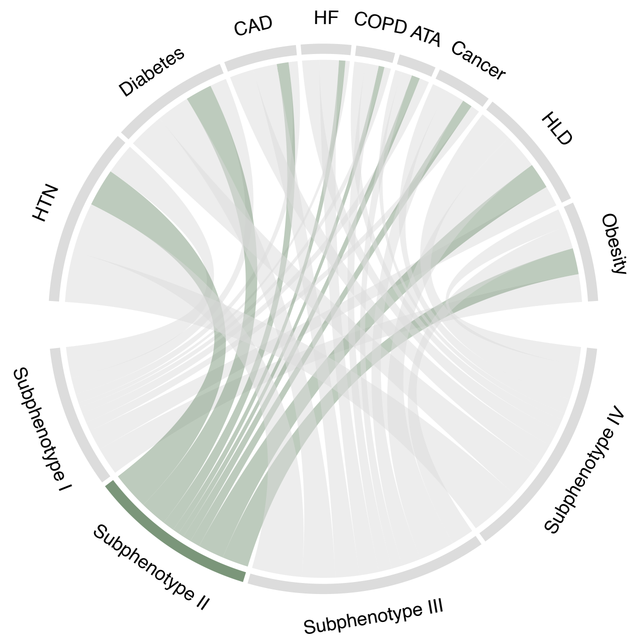
Comorbidity vs. subphenotypes



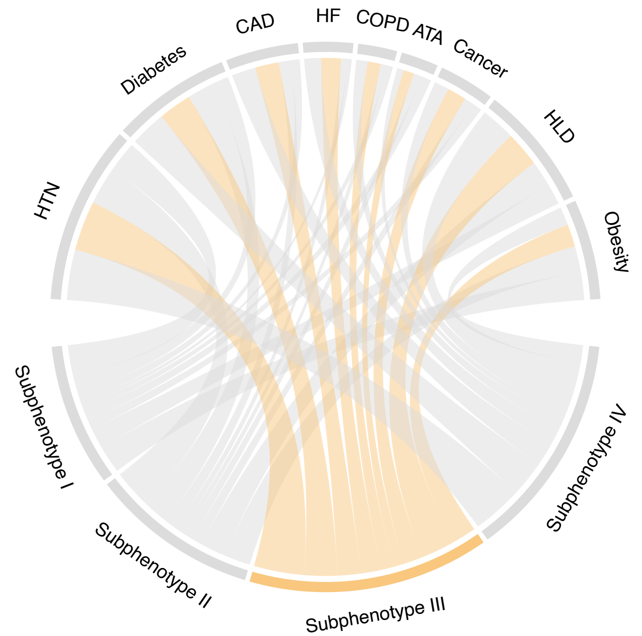
Comorbidity vs. Subphenotype I



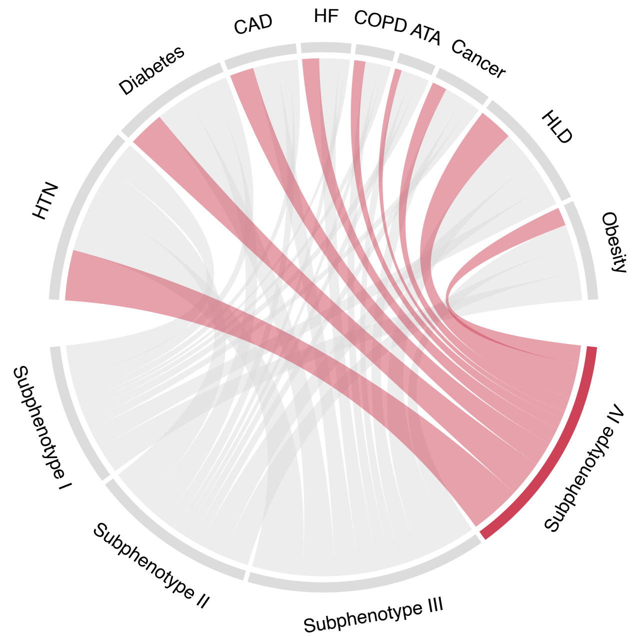
Comorbidity vs. Subphenotype II

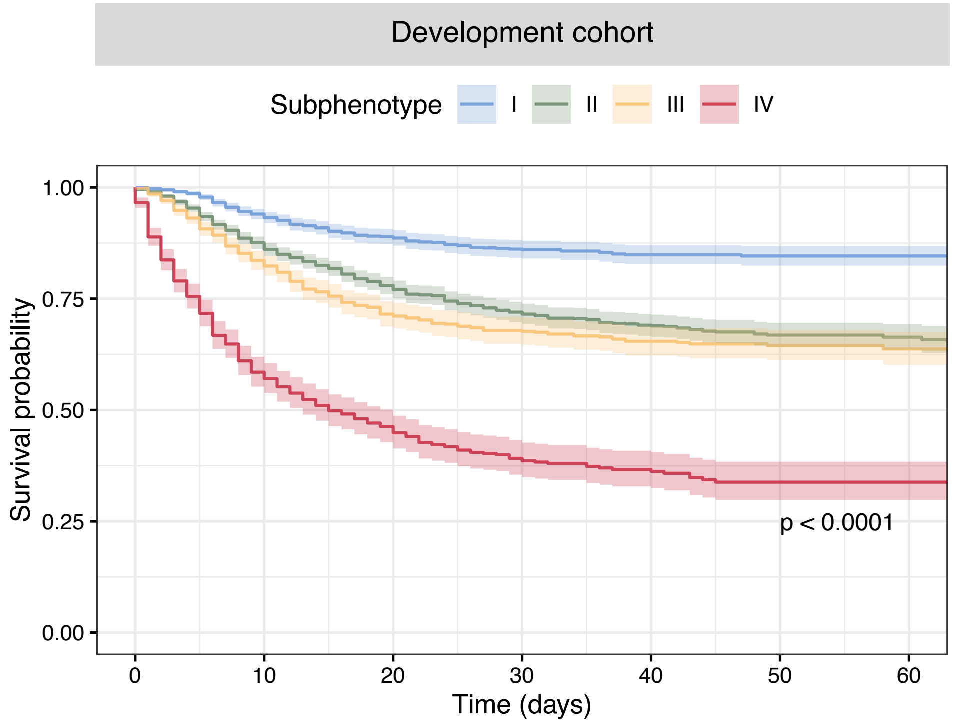


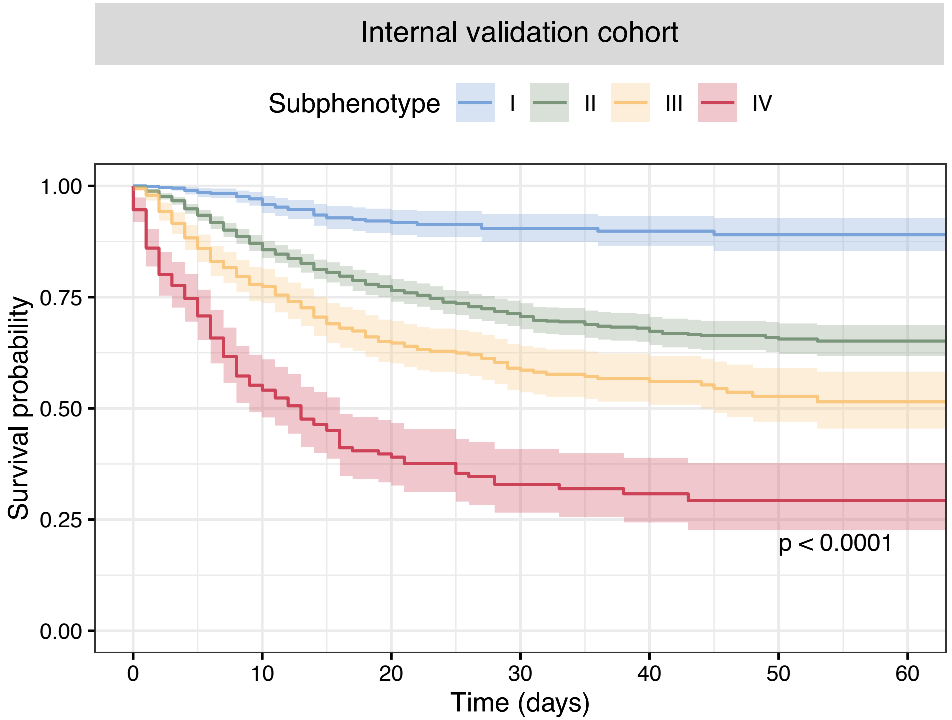
Comorbidity vs. Subphenotype III

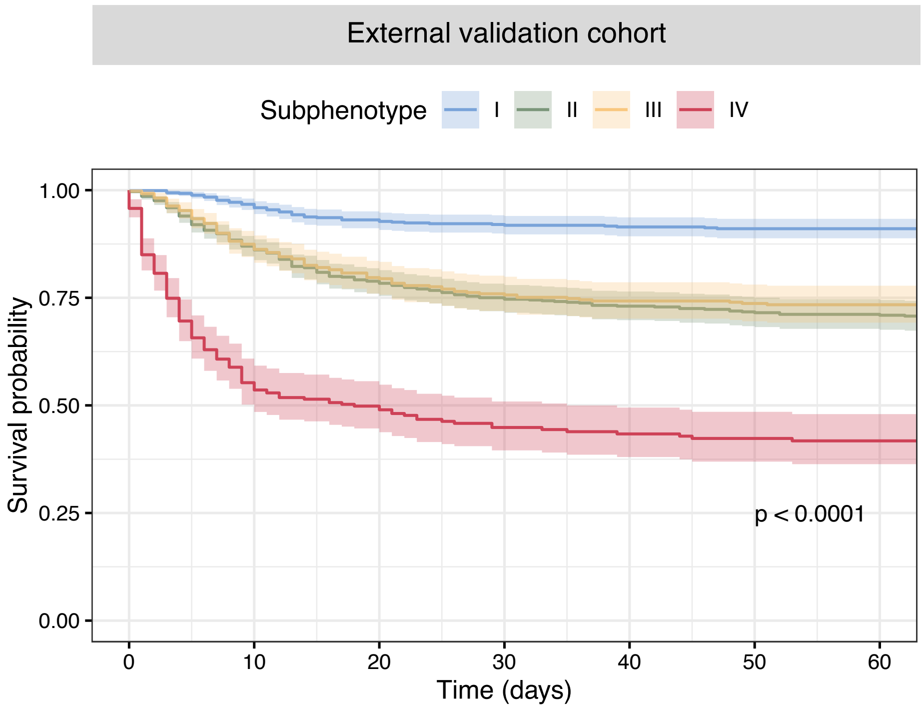


Comorbidity vs. Subphenotype IV




Development cohort
Subphenotype I II III IV
Survival probability
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60
Time (days)
p < 0.0001


Internal validation cohort
Subphenotype I II III IV
Survival probability
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60
Time (days)
p < 0.0001


External validation cohort
Subphenotype I II III IV
Survival probability
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60
Time (days)
p < 0.0001

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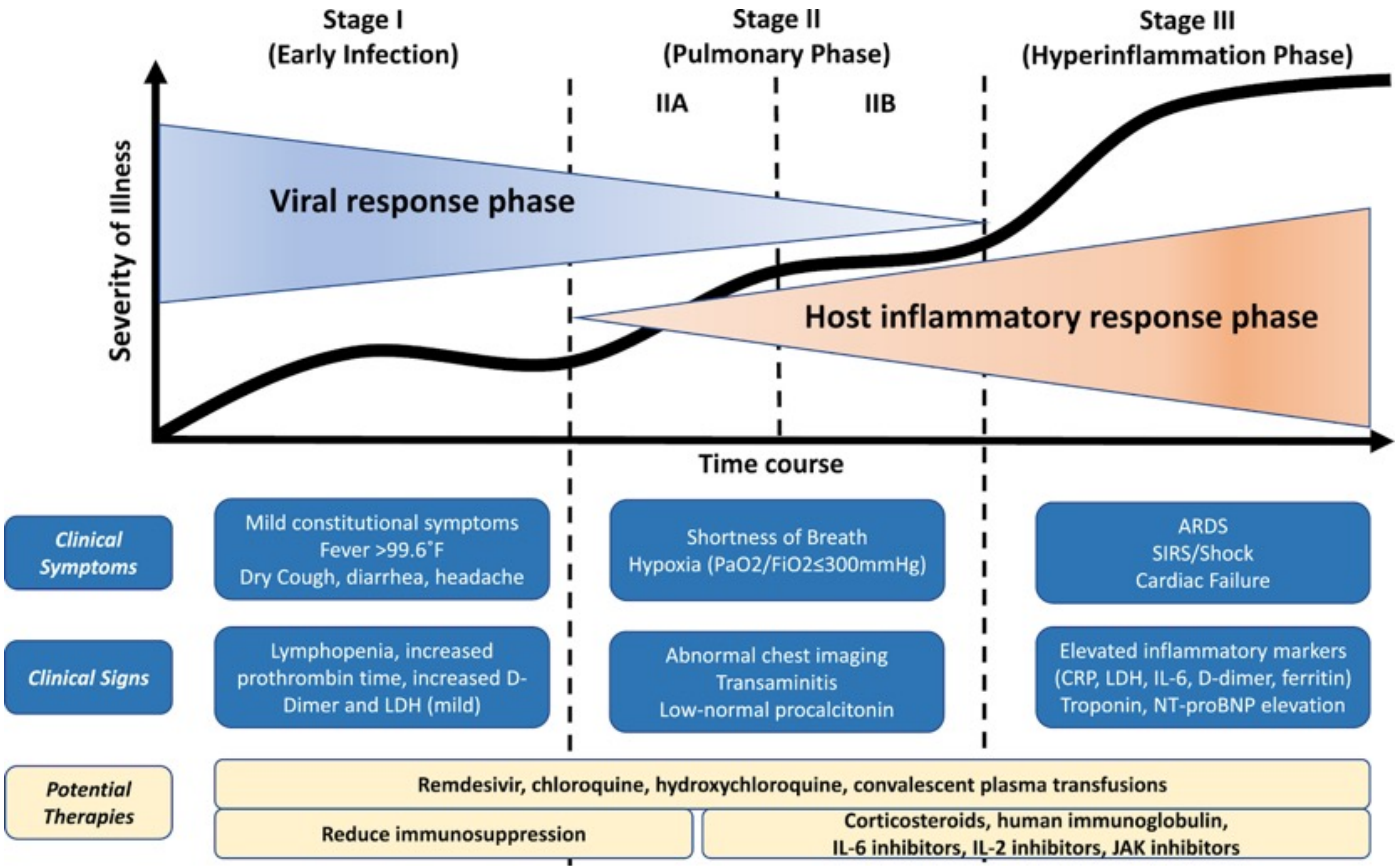
- Subphenotyping of Long COVID
- Subphenotyping of PD
- Discussions

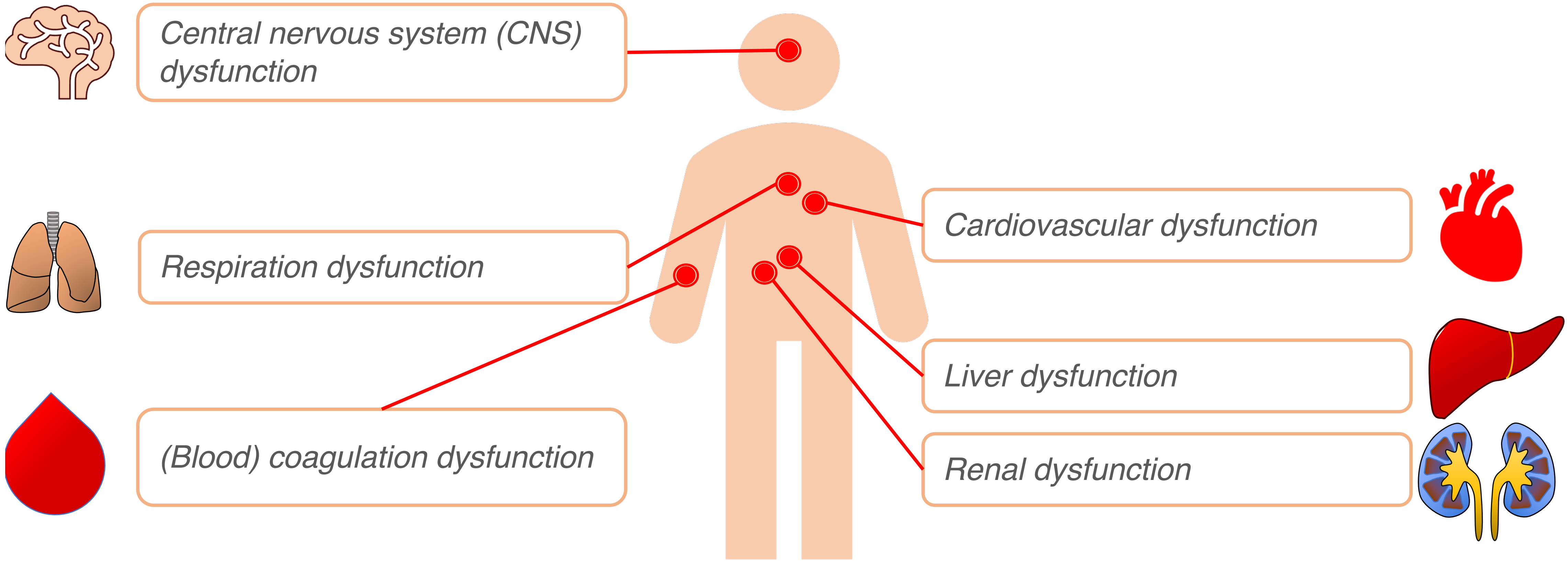
Su, Chang, Zhenxing Xu, Katherine Hoffman, Parag Goyal, Monika M. Safford, Jerry Lee, Sergio Alvarez-Mulett et al. "Identifying organ dysfunction trajectory-based subphenotypes in critically ill patients with COVID-19." *Scientific Reports* 11, no. 1 (2021): 15872.

An Early Conceptual Model for the Progression of COVID-19 in Acute Phase



Siddiqi, Hasan K., and Mandeep R. Mehra. "COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal." *The Journal of Heart and Lung Transplantation* 39, no. 5 (2020): 405.

Sequential Organ Failure Assessment



Cohort Setup

Mar 1^{st} to May 12^{th}

New York Presbyterian
Weill Cornell Medical Center
*(NYP-WCMC) – **348 patients***

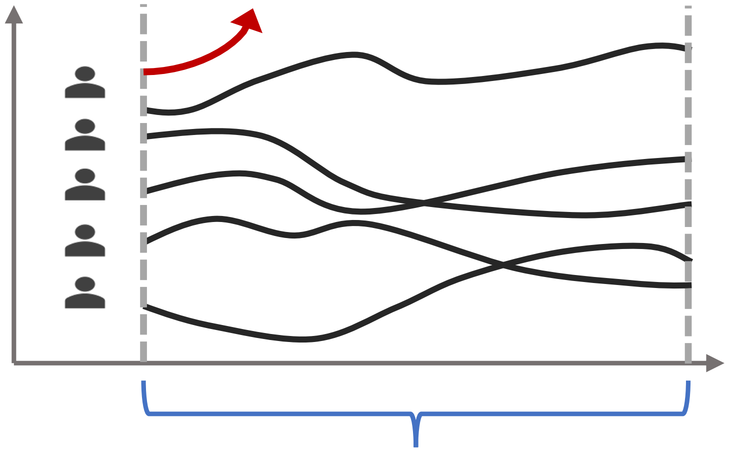
Development

New York Presbyterian
Lower Manhattan Hospital
*(NYP-LMH) – **100 patients***

Validation

Post-intubation SOFA trajectory

Intubation time

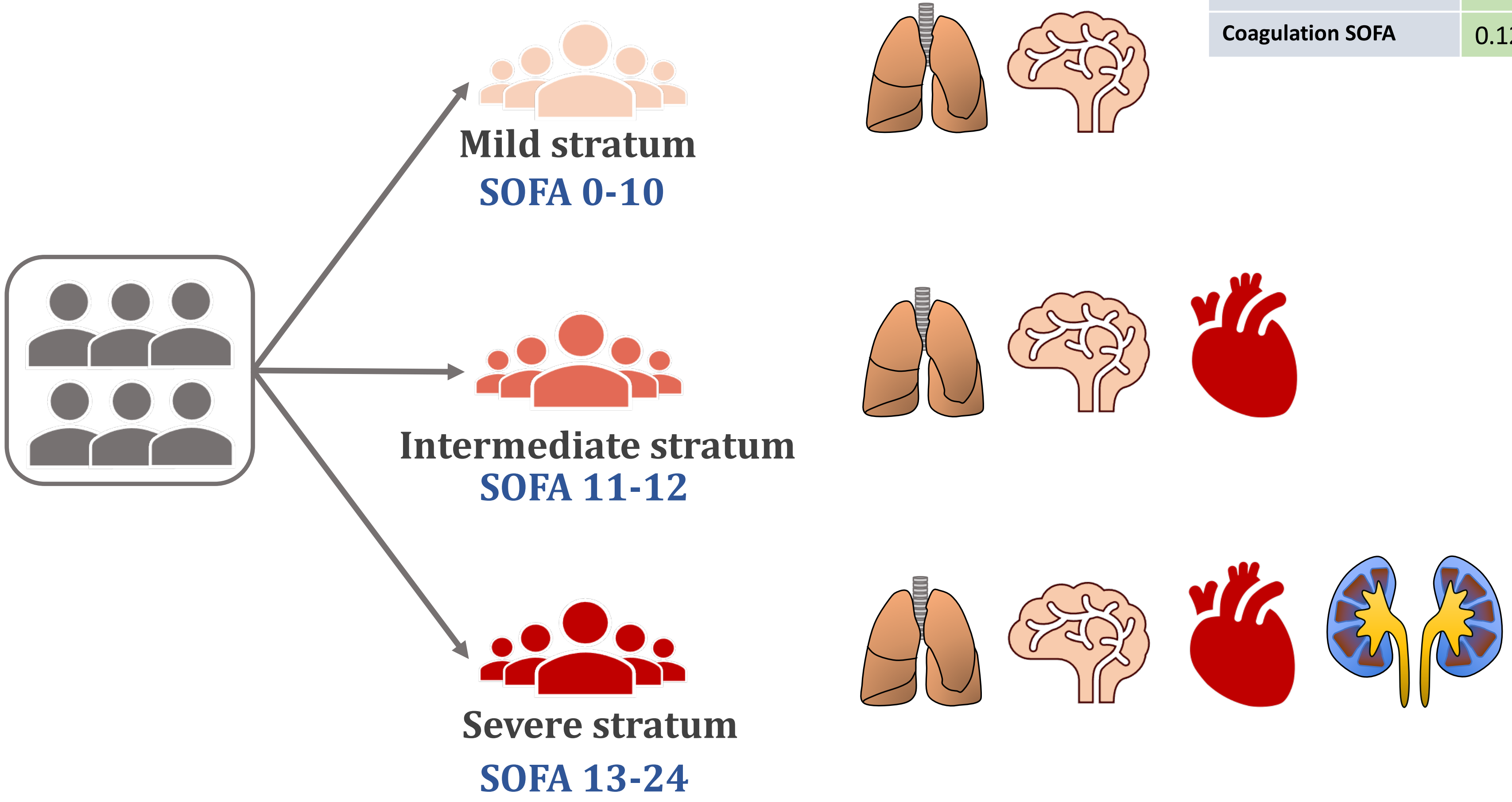


7-days window after intubation

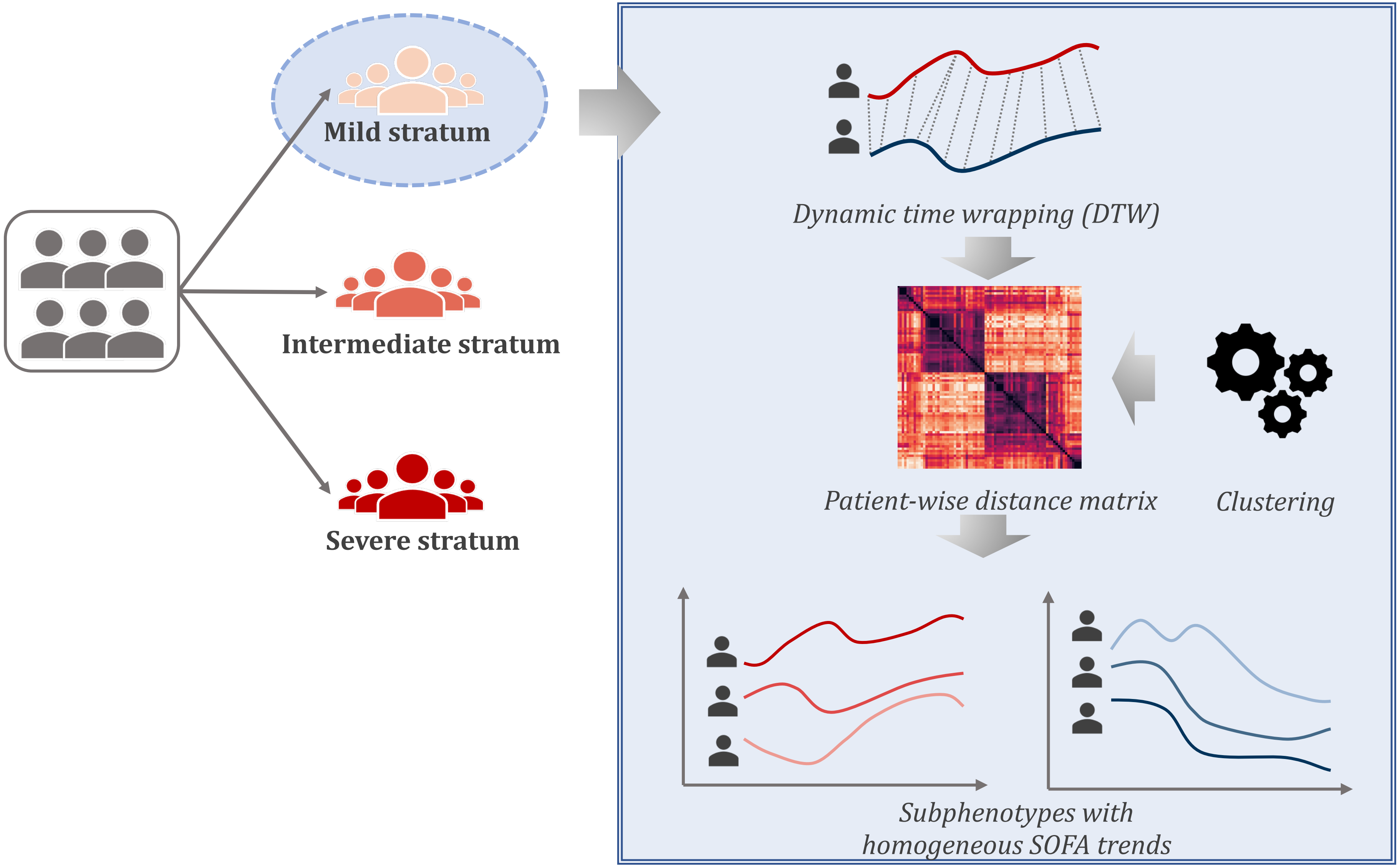
- SOFA scores were calculated every *24 hours*
- Patients missing more than 3-days SOFA data were excluded

Baseline Stratification

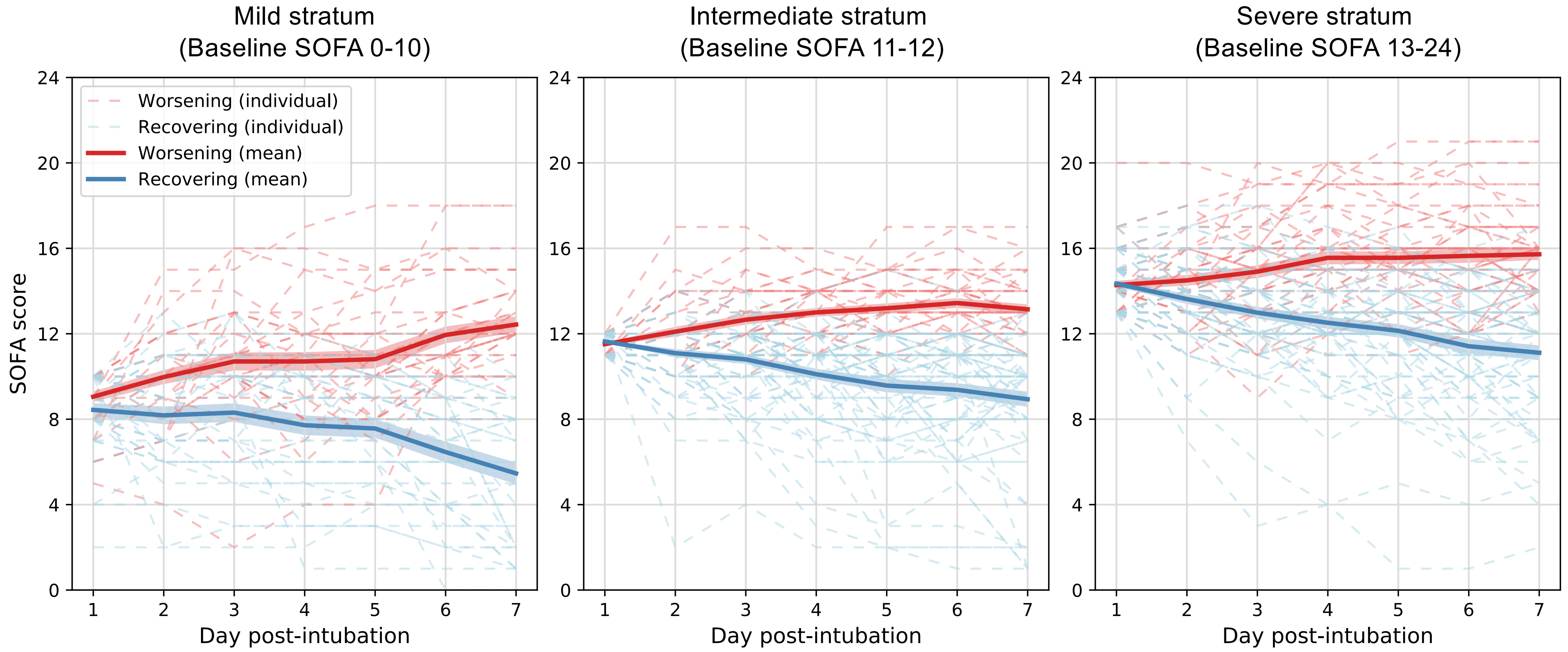
	Mild	Intermediate	Severe
Respiration SOFA	3.45 (0.89)	3.89 (0.45)	3.97 (0.25)
CNS SOFA	3.34 (1.13)	3.72 (0.47)	3.94 (0.24)
Cardiovascular SOFA	1.32 (1.34)	3.41 (0.88)	3.69 (0.70)
Renal SOFA	0.16 (0.54)	0.35 (0.67)	1.96 (1.44)
Liver SOFA	0.20 (0.46)	0.14 (0.43)	0.37 (0.67)
Coagulation SOFA	0.12 (0.40)	0.04 (0.20)	0.28 (0.64)



Trajectory Grouping



Identified Subphenotypes

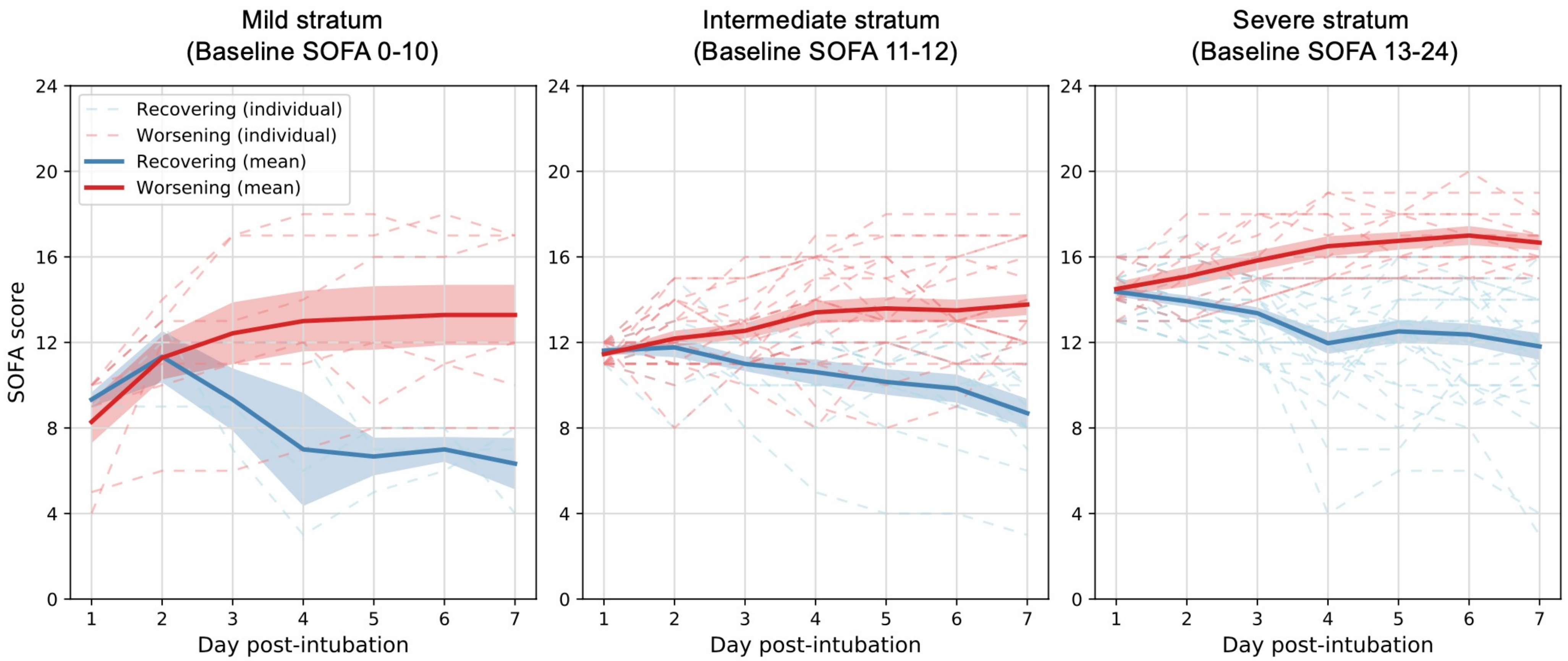


Worsening, n=37
Recovering, n=39

Worsening, n=41
Recovering, n=75

Worsening, n=54
Recovering, n=72

Identified Subphenotypes

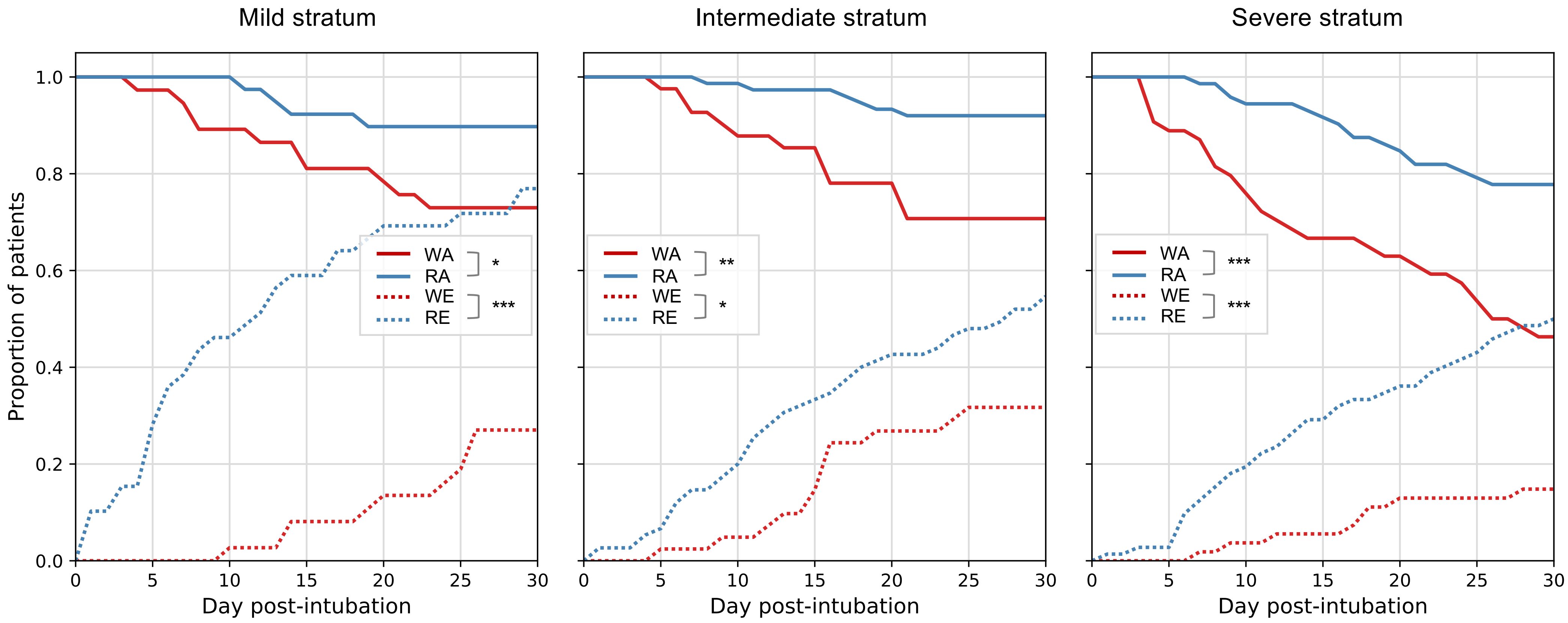


Worsening, n=7
Recovering, n=3

Worsening, n=22
Recovering, n=13

Worsening, n=12
Recovering, n=27

Association with Outcomes

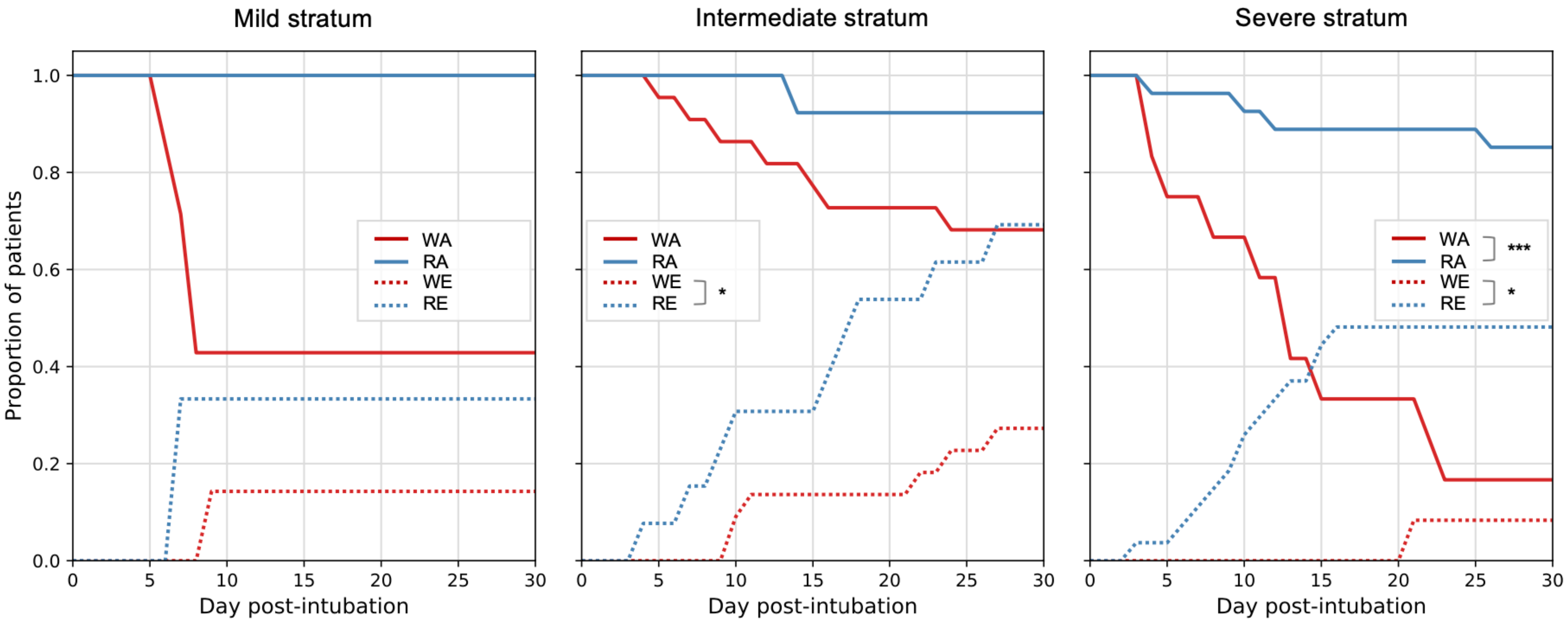


* $P < 0.05$
** $p < 0.01$
*** $p < 0.001$

Abbreviations: WA=worsening subphenotype alive; RA=recovering subphenotype alive;

WE=worsening subphenotype extubated; RE=recovering subphenotype extubated.

Association with Outcomes



* $P < 0.05$
** $p < 0.01$
*** $p < 0.001$

Abbreviations: WA=worsening subphenotype alive; RA=recovering subphenotype alive;

WE=worsening subphenotype extubated; RE=recovering subphenotype extubated.

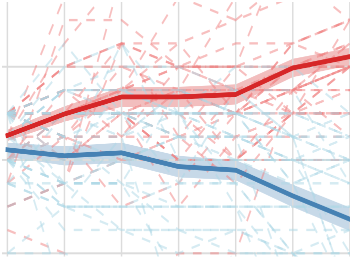
Discriminative Biomarker Identification

Baseline strata | *Subphenotype* | *Biomarkers*

Mild

Worsening

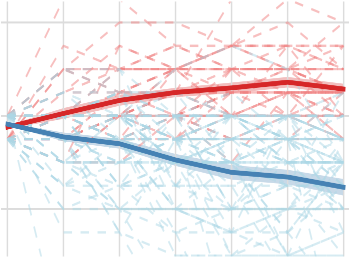
Recovering



Intermediate

Worsening

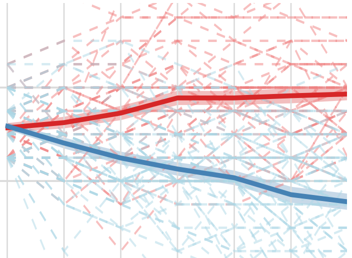
Recovering



Severe

Worsening

Recovering



- *27 laboratory test values*

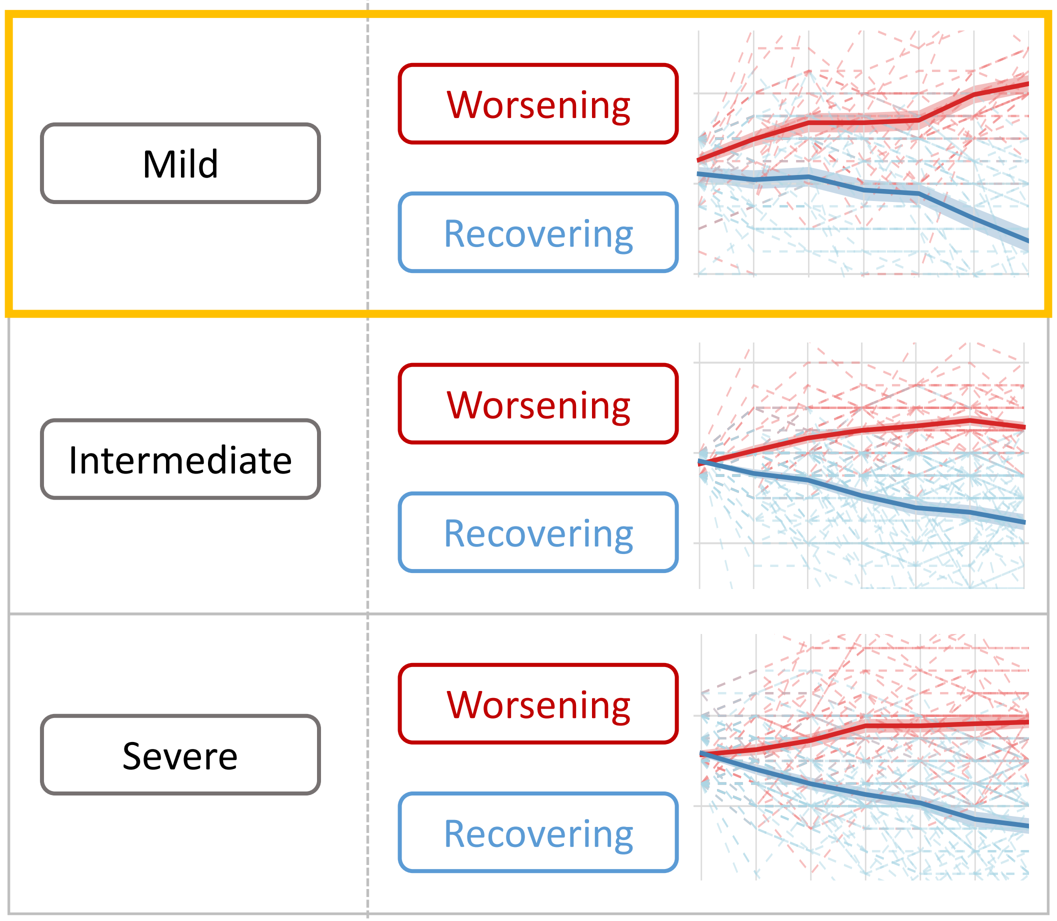
  E.g., albumin, bilirubin, and white blood cell count

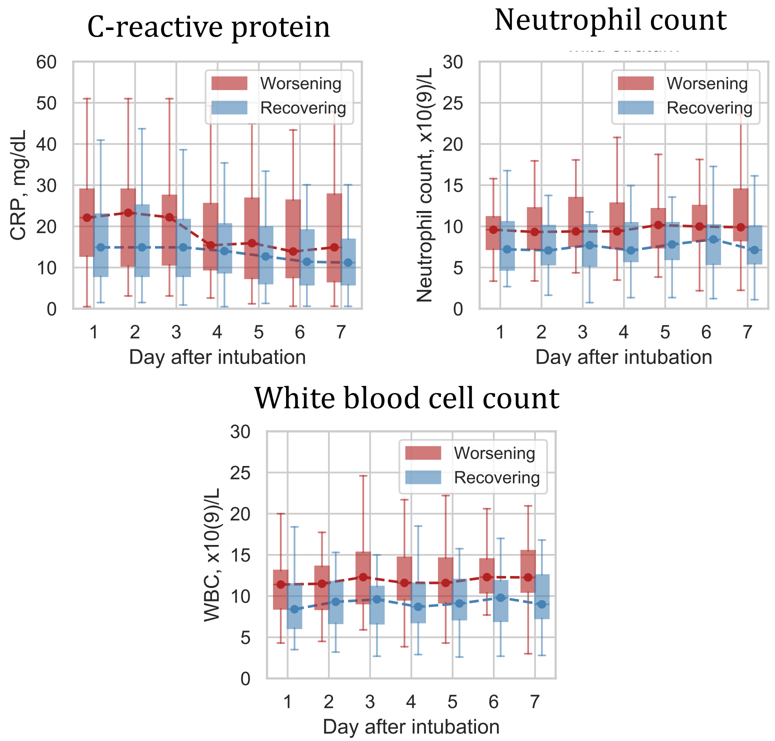
- *4 vital signs*

  Body temperature, urine output, mean arterial pressure, and Glasgow Coma Scale (GCS, consciousness)

Discriminative Biomarker Identification

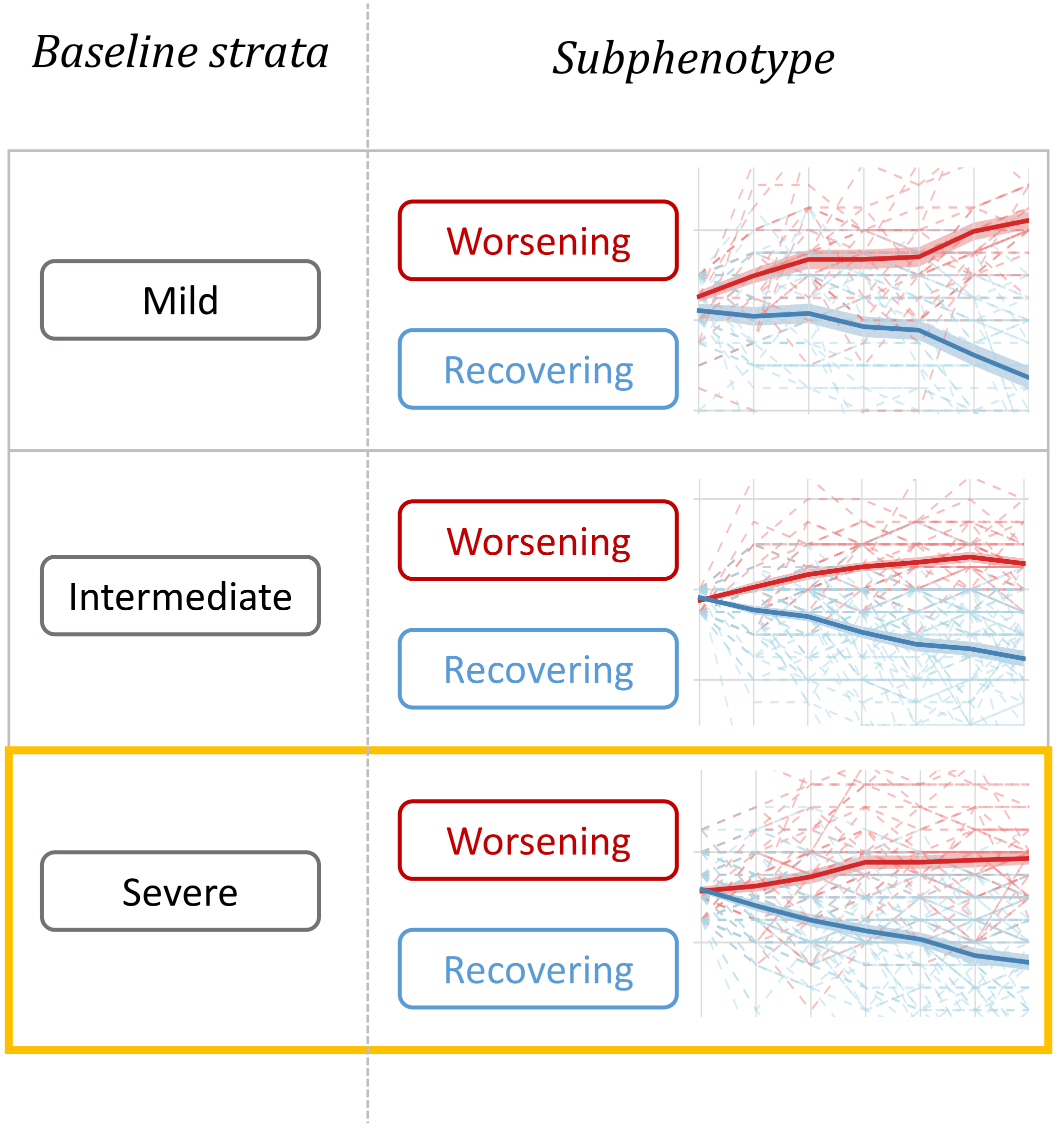
Baseline strata | *Subphenotype* | *Biomarkers*

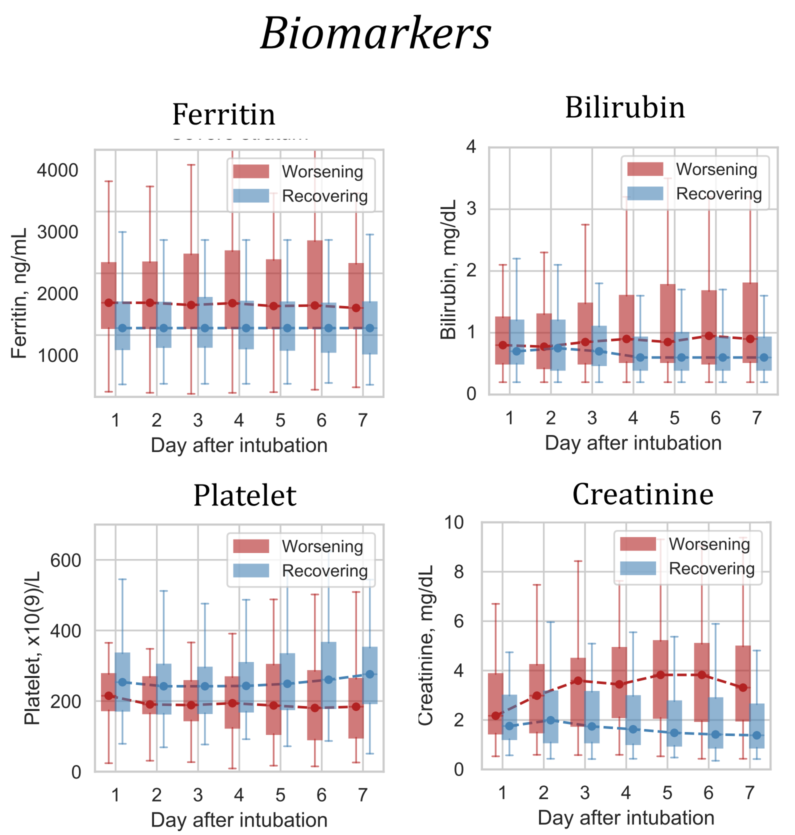




Inflammatory *hinders the worsening subphenotype from recovery.*

Discriminative Biomarker Identification





***Worsening** is driven by cell death, macrophage activation and overt organ dysfunction with disseminated intravascular coagulation*

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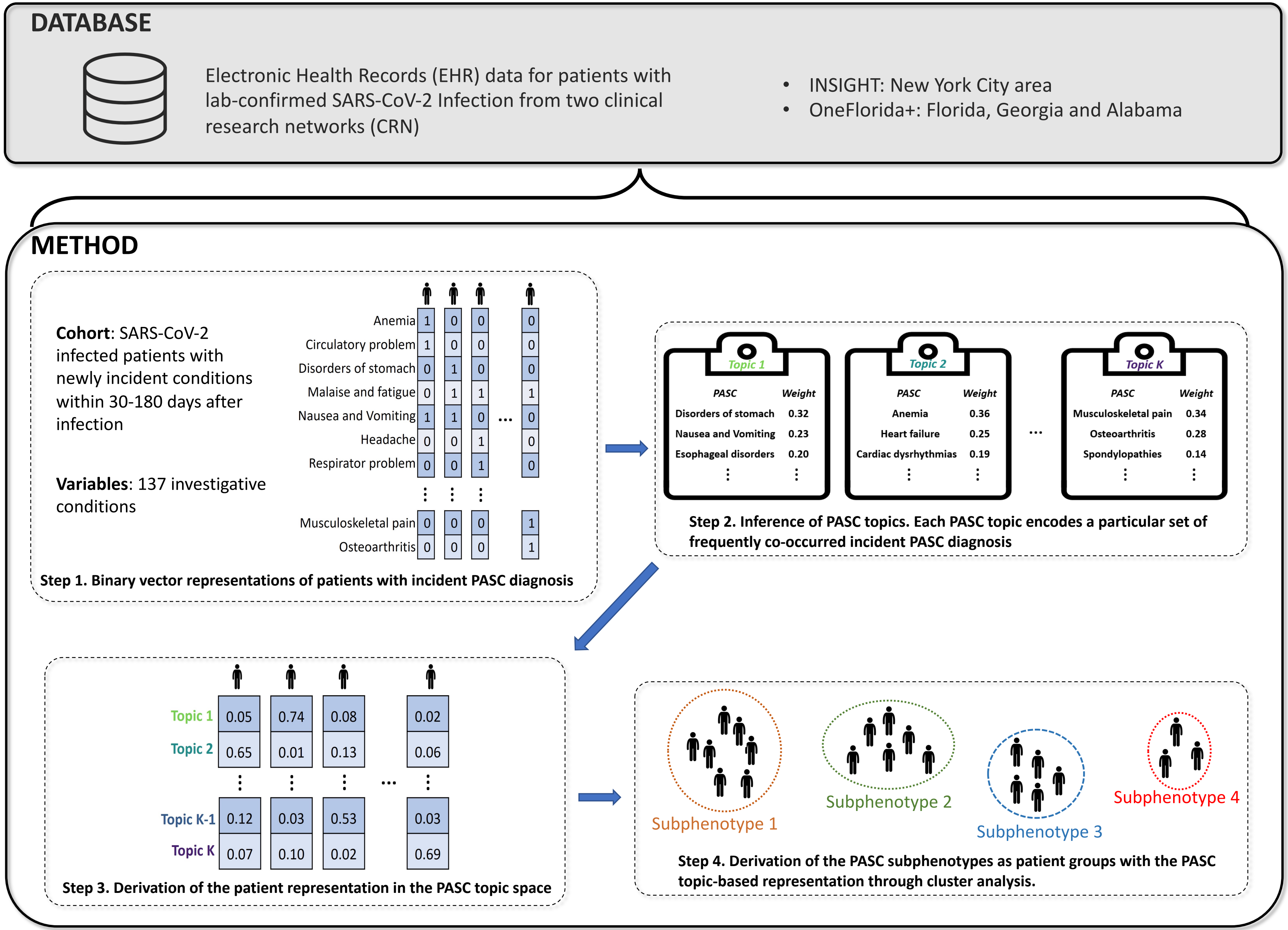
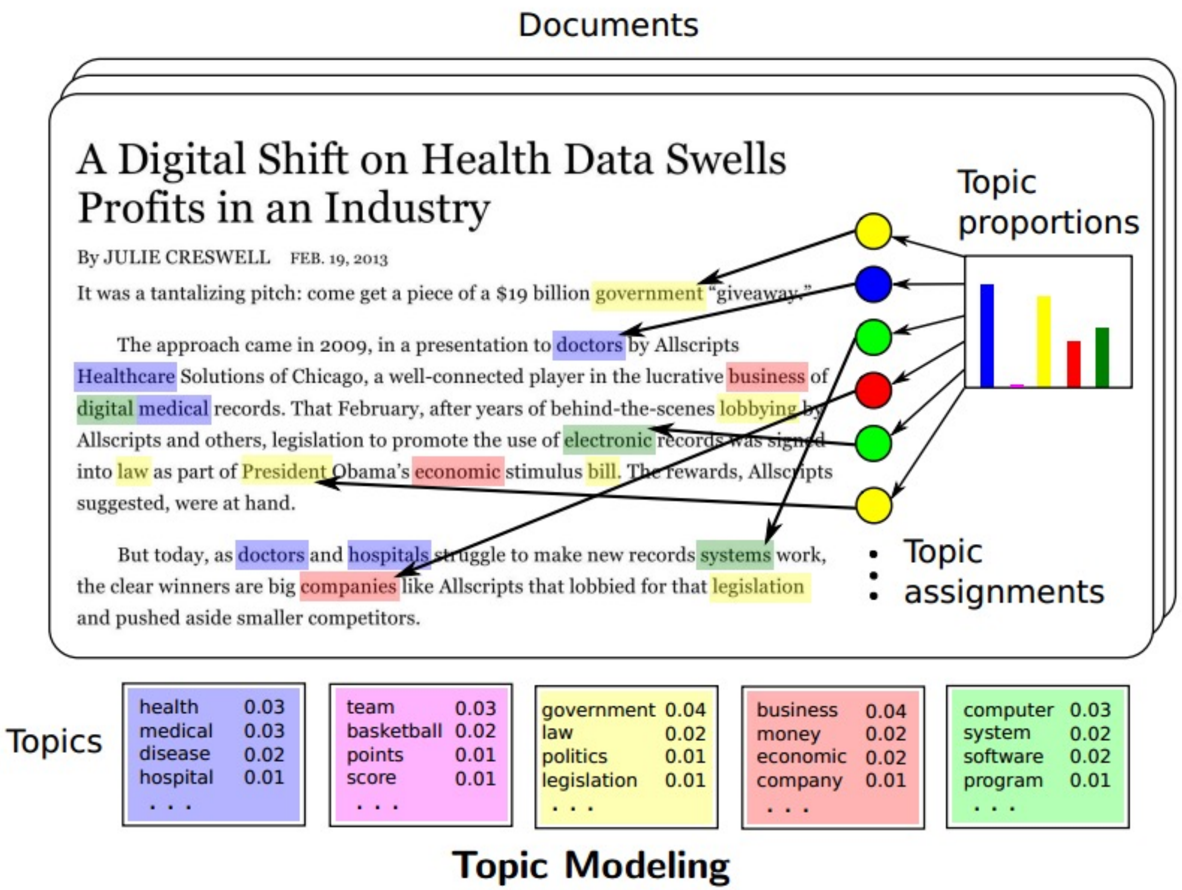
Zhang, Hao, Chengxi Zang, Zhenxing Xu, Yongkang Zhang, Jie Xu, Jiang Bian, Dmitry Morozyuk et al. "Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes." *Nature Medicine* 29, no. 1 (2023): 226-235.

Pipeline


DATABASE
Electronic Health Records (EHR) data for patients with lab-confirmed SARS-CoV-2 Infection from two clinical research networks (CRN)
• INSIGHT: New York City area
• OneFlorida+: Florida, Georgia and Alabama
METHOD
Cohort: SARS-CoV-2 infected patients with newly incident conditions within 30-180 days after infection
Variables: 137 investigative conditions
Anemia
Circulatory problem
Disorders of stomach
Malaise and fatigue
Nausea and Vomiting
Headache
Respirator problem
Musculoskeletal pain
Osteoarthritis
Step 1. Binary vector representations of patients with incident PASC diagnosis
Topic 1
PASC Weight
Disorders of stomach 0.32
Nausea and Vomiting 0.23
Esophageal disorders 0.20
Topic 2
PASC Weight
Anemia 0.36
Heart failure 0.25
Cardiac dysrhythmias 0.19
Topic K
PASC Weight
Musculoskeletal pain 0.34
Osteoarthritis 0.28
Spondylopathies 0.14
Step 2. Inference of PASC topics. Each PASC topic encodes a particular set of frequently co-occurred incident PASC diagnosis
Topic 1 0.05 0.74 0.08 0.02
Topic 2 0.65 0.01 0.13 0.06
Topic K-1 0.12 0.03 0.53 0.03
Topic K 0.07 0.10 0.02 0.69
Step 3. Derivation of the patient representation in the PASC topic space
Subphenotype 1
Subphenotype 2
Subphenotype 3
Subphenotype 4
Step 4. Derivation of the PASC subphenotypes as patient groups with the PASC topic-based representation through cluster analysis.

Background – probabilistic topic modeling



- **Topics**: a distribution over all words. Global parameters shared by all documents.

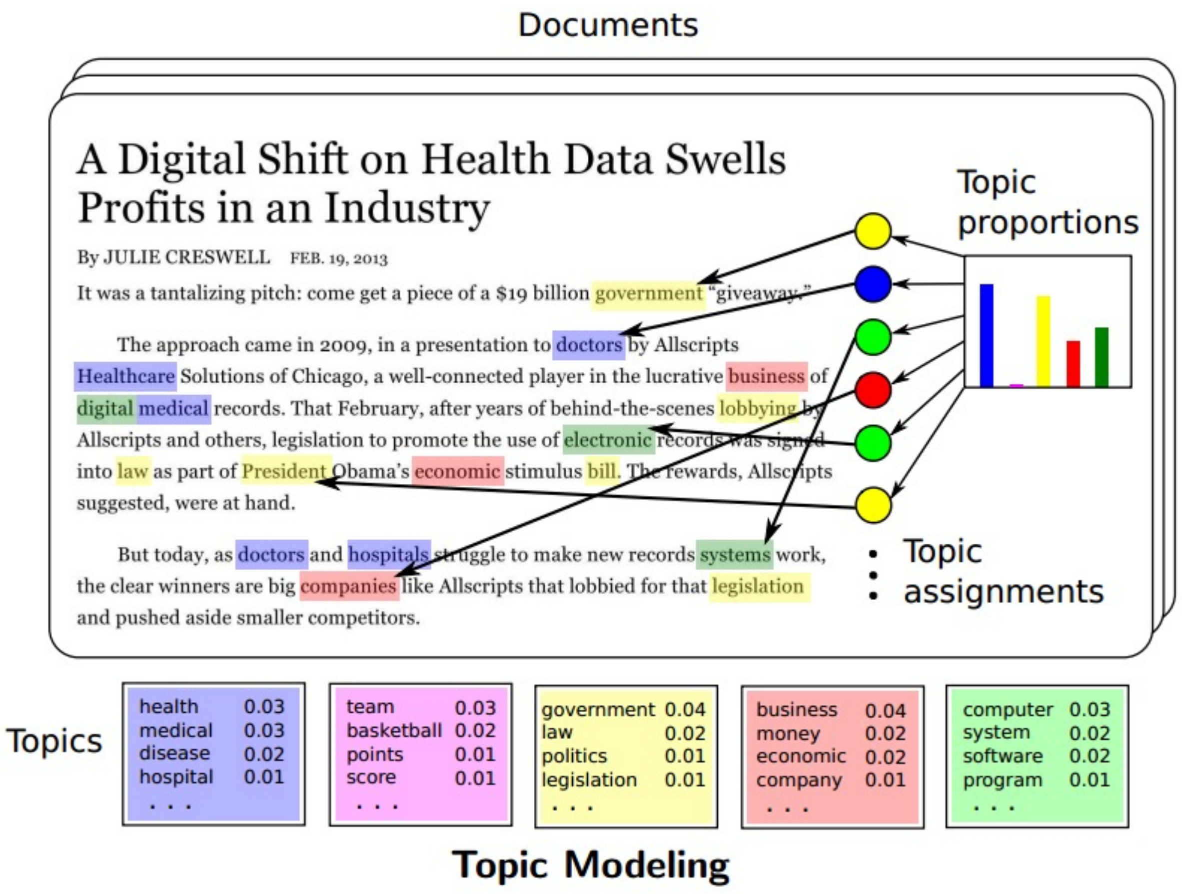
- **Topic proportion**: represent the importance of each topic in representing this document. Local parameters denotes the new feature of each document in topic space.

Transform the document represented by words to a new feature represented by topics.

The basic idea of topic modeling: exploring different topics (group of some "similar" words) for documents

Similar (word cooccurrence): some words should often appear simultaneously in one document

Background – probabilistic topic modeling



Topic modeling	PCA
Topics	Factors
Topic proportion	Factor loading

Transform the document represented by words to a new feature represented by topics.

Vocabulary	1)	2)
industry	3	0
NBA	0	6
economy	2	1
economic	3	2
game	0	5
medical	2	0
business	3	4
...		...

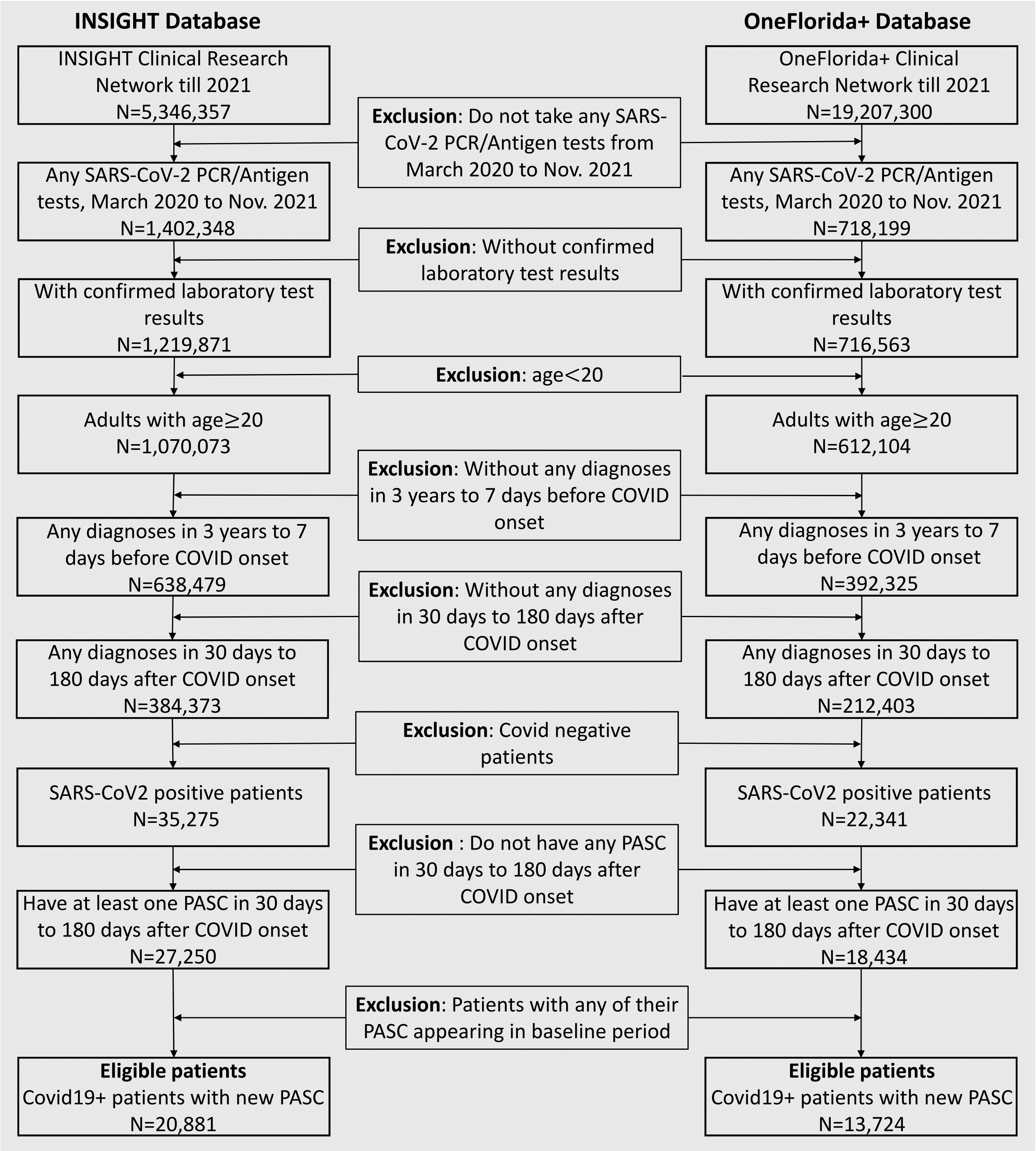
This vector should be high-dimensional, sparse, and discrete.

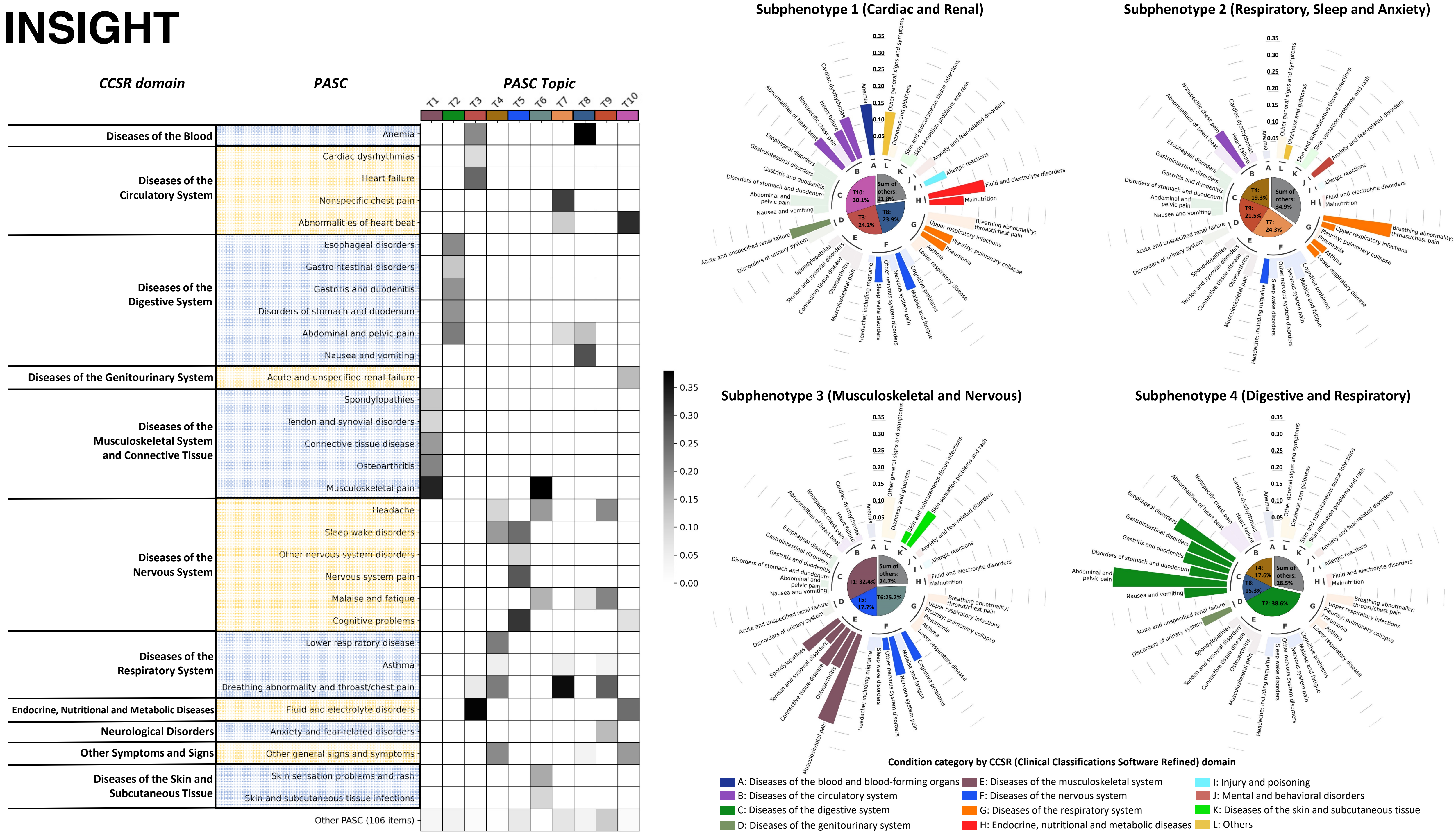
VS

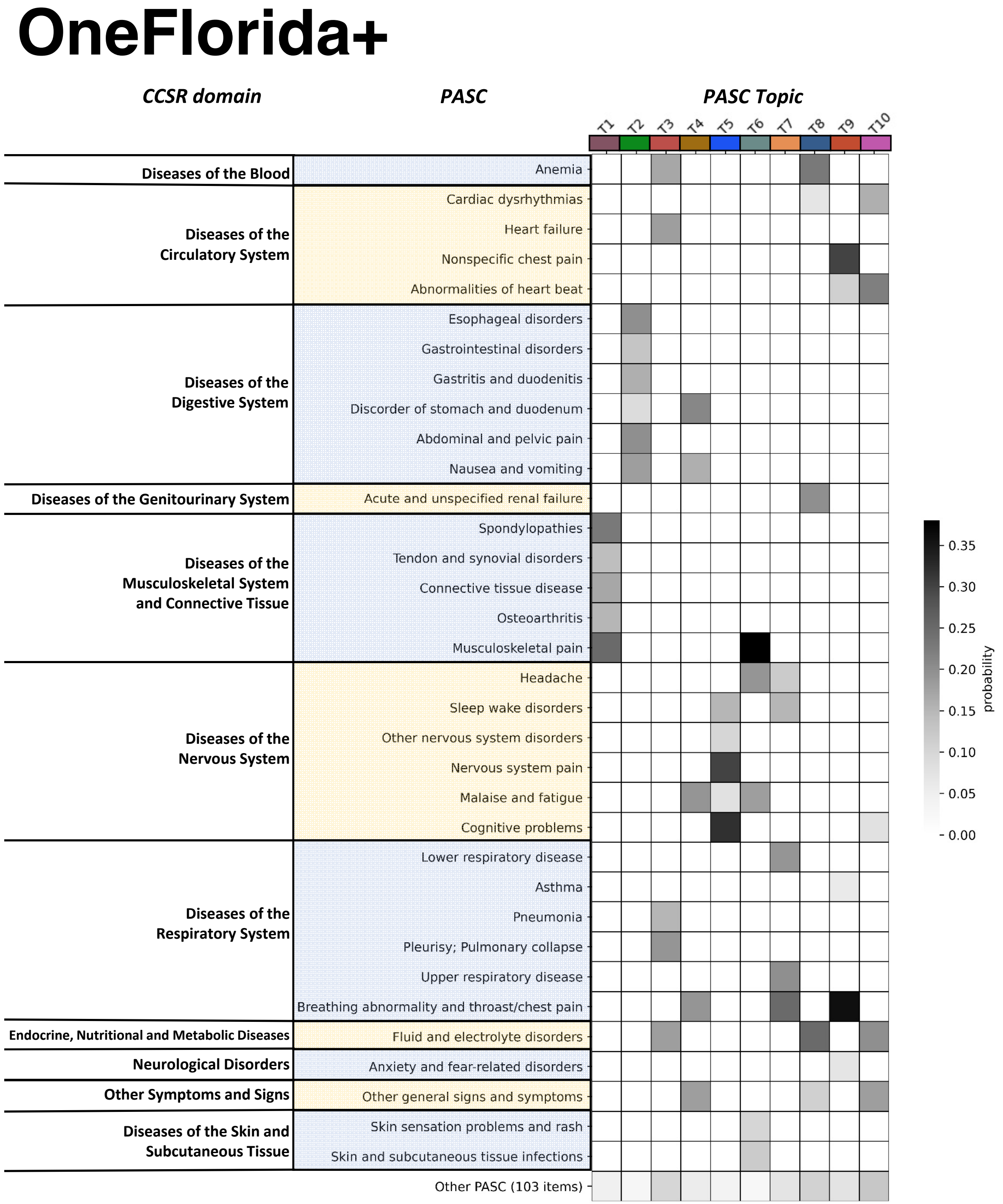
Vocabulary	1)	2)
Topic1	0.4	0.05
Topic2	0.06	0.3
Topic3	0.3	0.04
Topic4	0.05	0.3
Topic5	0.19	0.31

This vector should be low-dimensional, dense, and continuous

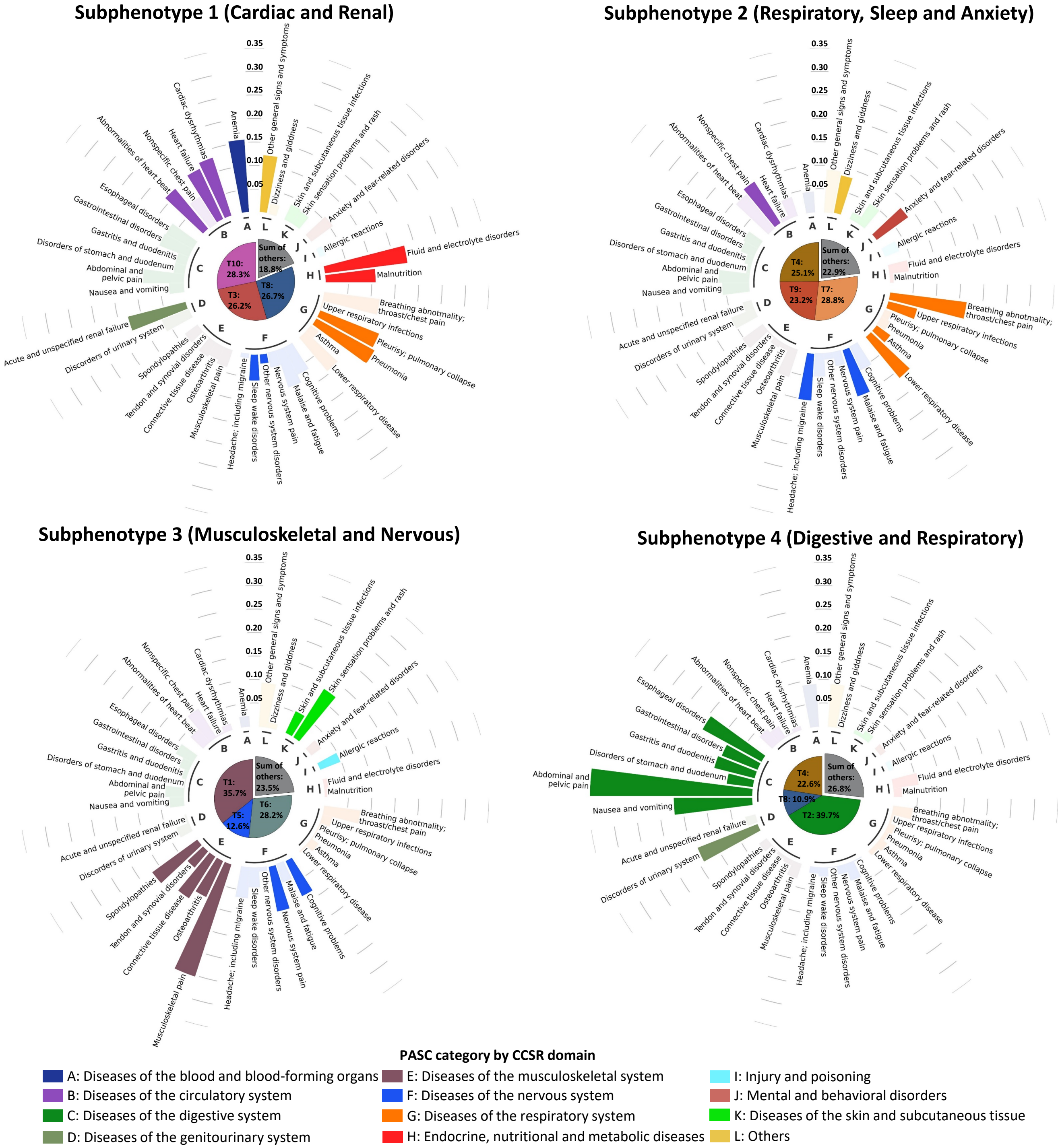
Inclusion-Exclusion cascade




INSIGHT
CCSR domain
PASC
PASC Topic
T1 T2 T3 T4 T5 T6 T7 T8 T9 T10
Diseases of the Blood
Anemia
Diseases of the Circulatory System
Cardiac dysrhythmias
Heart failure
Nonspecific chest pain
Abnormalities of heart beat
Diseases of the Digestive System
Esophageal disorders
Gastrointestinal disorders
Gastritis and duodenitis
Disorders of stomach and duodenum
Abdominal and pelvic pain
Nausea and vomiting
Diseases of the Genitourinary System
Acute and unspecified renal failure
Diseases of the Musculoskeletal System and Connective Tissue
Spondylopathies
Tendon and synovial disorders
Connective tissue disease
Osteoarthritis
Musculoskeletal pain
Diseases of the Nervous System
Headache
Sleep wake disorders
Other nervous system disorders
Nervous system pain
Malaise and fatigue
Cognitive problems
Diseases of the Respiratory System
Lower respiratory disease
Asthma
Breathing abnormality and throat/chest pain
Endocrine, Nutritional and Metabolic Diseases
Fluid and electrolyte disorders
Neurological Disorders
Anxiety and fear-related disorders
Other Symptoms and Signs
Other general signs and symptoms
Diseases of the Skin and Subcutaneous Tissue
Skin sensation problems and rash
Skin and subcutaneous tissue infections
Other PASC (106 items)
0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
Subphenotype 1 (Cardiac and Renal)
T10: 30.1%
Sum of others: 21.8%
T8: 23.9%
T3: 24.2%
Subphenotype 2 (Respiratory, Sleep and Anxiety)
T4: 19.3%
Sum of others: 34.9%
T9: 21.5%
T7: 24.3%
Subphenotype 3 (Musculoskeletal and Nervous)
T1: 32.4%
Sum of others: 24.7%
T5: 17.7%
T6: 25.2%
Subphenotype 4 (Digestive and Respiratory)
T4: 17.6%
Sum of others: 28.5%
T8: 15.3%
T2: 38.6%
Condition category by CCSR (Clinical Classifications Software Refined) domain
A: Diseases of the blood and blood-forming organs
B: Diseases of the circulatory system
C: Diseases of the digestive system
D: Diseases of the genitourinary system
E: Diseases of the musculoskeletal system
F: Diseases of the nervous system
G: Diseases of the respiratory system
H: Endocrine, nutritional and metabolic diseases
I: Injury and poisoning
J: Mental and behavioral disorders
K: Diseases of the skin and subcutaneous tissue
L: Others

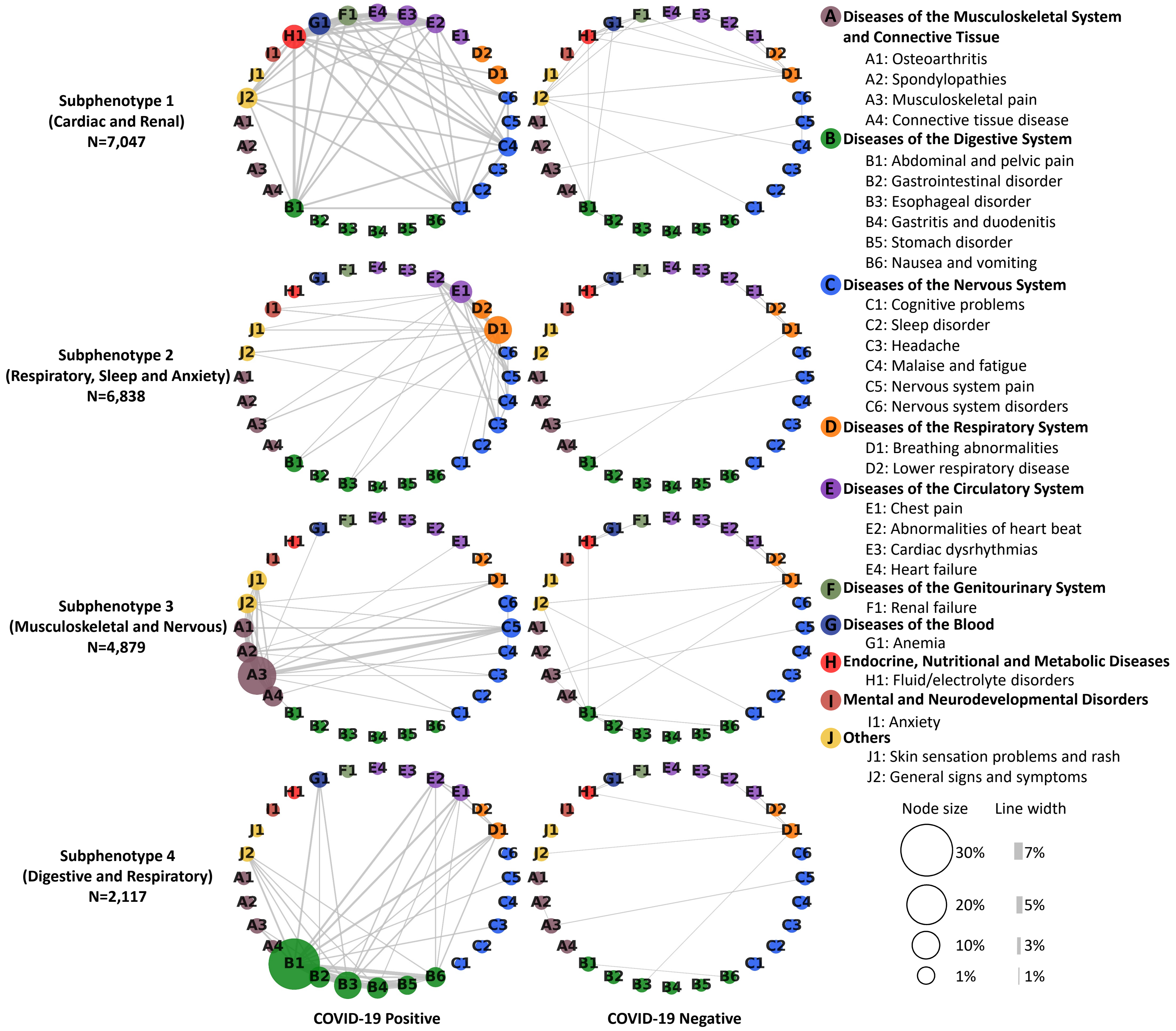


OneFlorida+
CCSR domain
PASC
PASC Topic
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
Diseases of the Blood
Anemia
Diseases of the Circulatory System
Cardiac dysrhythmias
Heart failure
Nonspecific chest pain
Abnormalities of heart beat
Diseases of the Digestive System
Esophageal disorders
Gastrointestinal disorders
Gastritis and duodenitis
Discorder of stomach and duodenum
Abdominal and pelvic pain
Nausea and vomiting
Diseases of the Genitourinary System
Acute and unspecified renal failure
Diseases of the Musculoskeletal System and Connective Tissue
Spondylopathies
Tendon and synovial disorders
Connective tissue disease
Osteoarthritis
Musculoskeletal pain
Diseases of the Nervous System
Headache
Sleep wake disorders
Other nervous system disorders
Nervous system pain
Malaise and fatigue
Cognitive problems
Diseases of the Respiratory System
Lower respiratory disease
Asthma
Pneumonia
Pleurisy; Pulmonary collapse
Upper respiratory disease
Breathing abnormality and throast/chest pain
Endocrine, Nutritional and Metabolic Diseases
Fluid and electrolyte disorders
Neurological Disorders
Anxiety and fear-related disorders
Other Symptoms and Signs
Other general signs and symptoms
Diseases of the Skin and Subcutaneous Tissue
Skin sensation problems and rash
Skin and subcutaneous tissue infections
Other PASC (103 items)
probability
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00

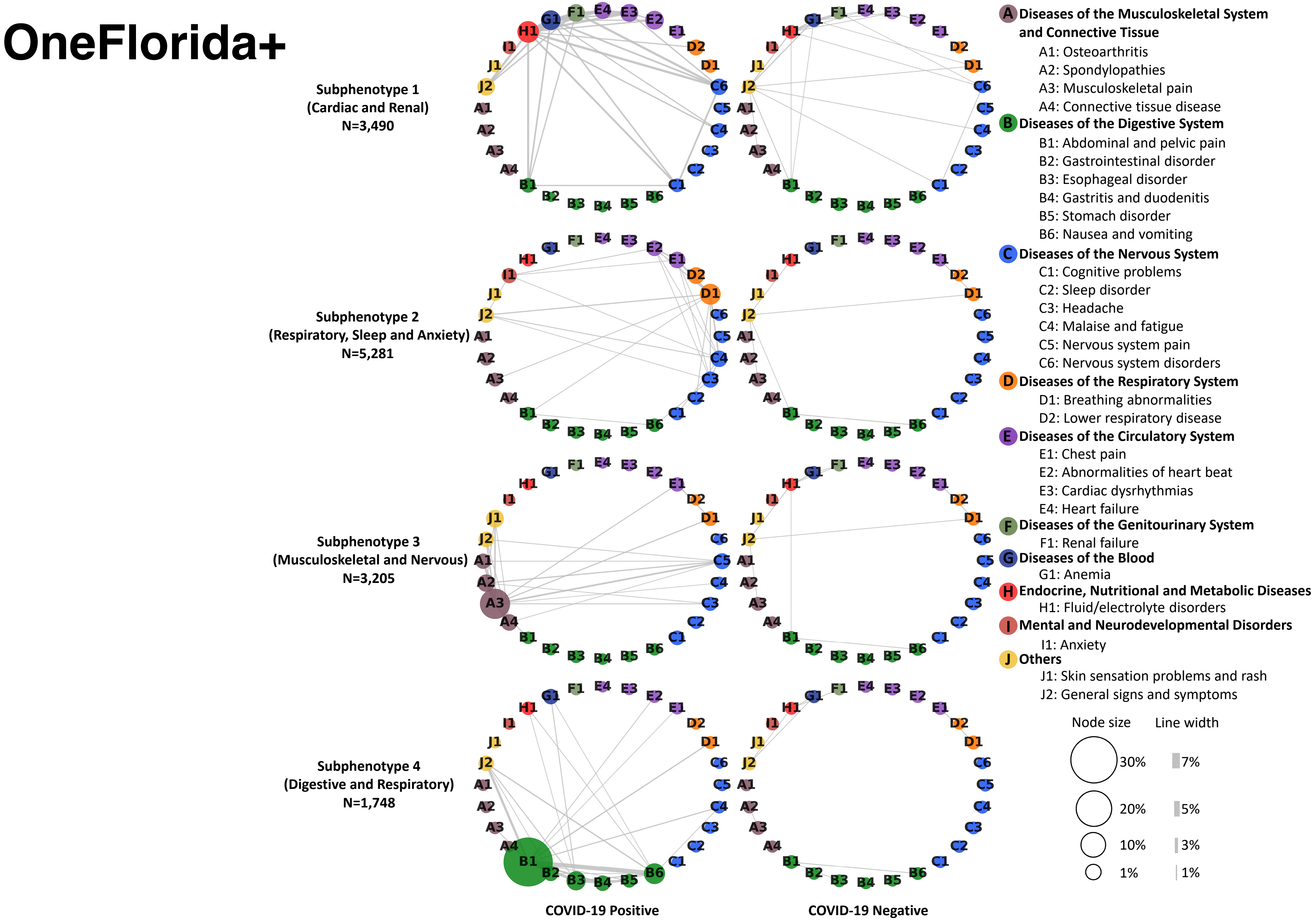


Subphenotype 1 (Cardiac and Renal)
T10: 28.3%
Sum of others: 18.8%
T3: 26.2%
T8: 26.7%
Subphenotype 2 (Respiratory, Sleep and Anxiety)
T4: 25.1%
Sum of others: 22.9%
T9: 23.2%
T7: 28.8%
Subphenotype 3 (Musculoskeletal and Nervous)
T1: 35.7%
Sum of others: 23.5%
T5: 12.6%
T6: 28.2%
Subphenotype 4 (Digestive and Respiratory)
T4: 22.6%
Sum of others: 26.8%
T8: 10.9%
T2: 39.7%
PASC category by CCSR domain
A: Diseases of the blood and blood-forming organs
B: Diseases of the circulatory system
C: Diseases of the digestive system
D: Diseases of the genitourinary system
E: Diseases of the musculoskeletal system
F: Diseases of the nervous system
G: Diseases of the respiratory system
H: Endocrine, nutritional and metabolic diseases
I: Injury and poisoning
J: Mental and behavioral disorders
K: Diseases of the skin and subcutaneous tissue
L: Others

INSIGHT



Subphenotype 1
(Cardiac and Renal)
N=7,047
Subphenotype 2
(Respiratory, Sleep and Anxiety)
N=6,838
Subphenotype 3
(Musculoskeletal and Nervous)
N=4,879
Subphenotype 4
(Digestive and Respiratory)
N=2,117
COVID-19 Positive
COVID-19 Negative
A Diseases of the Musculoskeletal System and Connective Tissue
A1: Osteoarthritis
A2: Spondylopathies
A3: Musculoskeletal pain
A4: Connective tissue disease
B Diseases of the Digestive System
B1: Abdominal and pelvic pain
B2: Gastrointestinal disorder
B3: Esophageal disorder
B4: Gastritis and duodenitis
B5: Stomach disorder
B6: Nausea and vomiting
C Diseases of the Nervous System
C1: Cognitive problems
C2: Sleep disorder
C3: Headache
C4: Malaise and fatigue
C5: Nervous system pain
C6: Nervous system disorders
D Diseases of the Respiratory System
D1: Breathing abnormalities
D2: Lower respiratory disease
E Diseases of the Circulatory System
E1: Chest pain
E2: Abnormalities of heart beat
E3: Cardiac dysrhythmias
E4: Heart failure
F Diseases of the Genitourinary System
F1: Renal failure
G Diseases of the Blood
G1: Anemia
H Endocrine, Nutritional and Metabolic Diseases
H1: Fluid/electrolyte disorders
I Mental and Neurodevelopmental Disorders
I1: Anxiety
J Others
J1: Skin sensation problems and rash
J2: General signs and symptoms
Node size
Line width
30%
20%
10%
1%
7%
5%
3%
1%


OneFlorida+
Subphenotype 1
(Cardiac and Renal)
N=3,490
Subphenotype 2
(Respiratory, Sleep and Anxiety)
N=5,281
Subphenotype 3
(Musculoskeletal and Nervous)
N=3,205
Subphenotype 4
(Digestive and Respiratory)
N=1,748
COVID-19 Positive
COVID-19 Negative
A Diseases of the Musculoskeletal System and Connective Tissue
A1: Osteoarthritis
A2: Spondylopathies
A3: Musculoskeletal pain
A4: Connective tissue disease
B Diseases of the Digestive System
B1: Abdominal and pelvic pain
B2: Gastrointestinal disorder
B3: Esophageal disorder
B4: Gastritis and duodenitis
B5: Stomach disorder
B6: Nausea and vomiting
C Diseases of the Nervous System
C1: Cognitive problems
C2: Sleep disorder
C3: Headache
C4: Malaise and fatigue
C5: Nervous system pain
C6: Nervous system disorders
D Diseases of the Respiratory System
D1: Breathing abnormalities
D2: Lower respiratory disease
E Diseases of the Circulatory System
E1: Chest pain
E2: Abnormalities of heart beat
E3: Cardiac dysrhythmias
E4: Heart failure
F Diseases of the Genitourinary System
F1: Renal failure
G Diseases of the Blood
G1: Anemia
H Endocrine, Nutritional and Metabolic Diseases
H1: Fluid/electrolyte disorders
I Mental and Neurodevelopmental Disorders
I1: Anxiety
J Others
J1: Skin sensation problems and rash
J2: General signs and symptoms
Node size
Line width
30%
7%
20%
5%
10%
3%
1%
1%

Outline

- Introduction
- Subphenotyping of COVID-19 at infection confirmation
- Subphenotyping of Severe COVID-19 after Mechanical Ventilation
- Subphenotyping of Long COVID
- Discussions

Discussions

- Complicated diseases are heterogeneous
  - Snapshot
  - Longitudinal
- Identification of disease subphenotypes from patients’ clinical data can help us better understand the clinical heterogeneity and trigger stratified medicine
- The next step is to “validate” the subphenotypes
  - External validation on independent data
  - Mechanism investigation
  - Treatment response assessments

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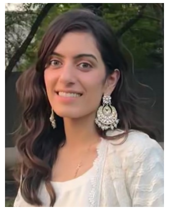

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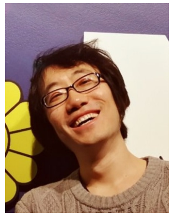

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https://wcm-wanglab.github.io/index.html

Thank You!

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